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FROM LITTLE ACORNS*

Presidential Address

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OBSTETRICS has matured slowly through a prolonged infancy and an adolescence beset by many conflicts. During its infancy, it was deserted by the medical profession, an unwanted child left in the hands of midwives and any others who wished to assume the prerogatives. Physicians would not practice the art because they considered it beneath their dignity. Its lowly and desperate state can be epitomized by a single act—in Germany in 1580, it became necessary to pass a law forbidding shepherds and herdsmen from attending obstetrical patients.[1]

In adolescence, it was adopted by surgeons, but they did not love and nourish it as their own child; they only tolerated it. Their true opinion is not reflected by the fact that they consummated the adoption, but rather is shown by their subsequent acts. For example, the old Charter of the Royal College of Surgeons provided that *no Fellow was eligible to a seat on the Council if he had practiced midwifery within five years.* Wistar, who was appointed to succeed William Shippen, Jr., as Professor of Surgery and Midwifery at the Medical College of Philadelphia (later to become the University of Pennsylvania), had no interest in obstetrics and promptly had a Chair of Obstetrics established separate from surgery. Thus, the surgeons in this country literally pitched obstetrics into adult life, not from a parent's desire to see the offspring flourish, but because of a persistent antipathy to it.

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Since obstetrics, with all the normal instincts of an adolescent child, had been making every effort to become independent of its adopted parent, the opportunity was quickly seized and by 1850 obstetric departments were established in most medical schools in this country. The surgeons generously permitted obstetrics to take along its small, very immature sister, gynecology. This was not considered a sacrifice because gynecology at that time was entirely medical. The obstetricians thus held the Chair of Obstetrics and Diseases (medical) of Women. Even today a few hospitals persist in maintaining a department composed of obstetrics and medical gynecology, a carry-over of now almost obscure traditions.

Obstetrics was also permitted to give medical care to the babies delivered because no one had any desire to take over this responsibility. Accordingly, The Chair of Obstetrics included Pediatrics as well as Diseases (medical) of Women. Not until about 1890 did Pediatrics become a separate department. In some places the practice of obstetrics and pediatrics is still combined. The care of the newborn is still relegated to the obstetrician in many hospitals. The slowness of evolution is apparent in many fields of medicine.

The surgeons were unaware of the future consequences of their act in aiding and abetting the union of obstetrics and gynecology (medical). They did not foresee the potentialities until the advent and sudden surge of pelvic surgery in the latter half of the 19th century. Those interested in this special field fought for and slowly brought about the separation of gynecology from surgery, not in all places, but in sufficient number to solidify gynecology as a specialty. This was accomplished in spite of tremendous resistance on the part of the general surgeons. That the latter succeeded to a meager extent is evidenced by the fact that in three medical schools in the United States, and in some hospitals, gynecology remains a section of the division of general surgery. Repeated new but unsuccessful moves have been made to recapture gynecologic surgery as a part of abdominal surgery. This is no innovation since early in the existence of gynecology a few schools had the academic title, Professor of Abdominal Surgery and Gynecology.

Those men who developed gynecologic surgery were not interested in the medical diseases of women, and so were content to leave the practice of this portion of gynecology to the obstetricians. They were far from content, however, to leave any pelvic surgical conditions to the obstetrician. They aggressively attempted to take for themselves all the surgical procedures of obstetrics. They were willing, and even insistent, that the obstetricians conduct patients through the months of pregnancy and supervise the normal childbirths. They were equally insistent that, if the need for cesarean section arose or a third-degree tear occurred, the performance of the necessary surgical procedures belonged to the realm of gynecologic surgery.

The general surgeons agreed with the idea that the obstetrician should not perform any surgery, since they deemed themselves the best qualified to take over the surgical care. To this day vestiges of these conflicts are existent and in many places gynecologists or general surgeons perform the surgical procedures upon pregnant women. Thus, more abuse was heaped upon the stepchild,

obstetrics, by the parent, surgery, and the infant sister, gynecology, now grown adult and strong. Obstetrics has fought back, has trained its personnel in gynecologic surgery, and has qualified them and made them competent to perform all obstetric procedures, both medical and surgical.

During the past twenty-five years the medical aspects of gynecology have advanced rapidly and have become the major activity in this field. The surgical horizons, although spreading widely, have not supplanted and cannot push aside or surpass the importance or the absolute necessity of medical gynecology.

During the rise of obstetrics and gynecology, special societies were organized which not only advanced the science, the knowledge, and the prestige of these fields of medicine, but also brought about over the years, through fraternization of their members, more communal thinking, ideals, and finally, unity.

The grouping of obstetrics and gynecology into a single division in the medical schools has aided in molding this unity. Combined departments of obstetrics and gynecology existed in 60 per cent of the medical schools in 1934.[2] By 1945 this percentage had increased to 73.[3] At present in the 72 medical schools in this country 56 (78 per cent) have combined departments. The following statistics are added here merely as a matter of information. In ten schools obstetrics and gynecology are separate and equal departments (14 per cent). In three schools obstetrics and gynecology are combined but are a division of general surgery (4 per cent). In three schools gynecology is a branch of general surgery and obstetrics is a separate department unto itself (4 per cent).

In those schools that have retained separate departments of obstetrics and gynecology, the integration and cooperation of the two are so intimate that they actually function as a unit. The aggression of the past has been replaced by amity. Bilateral training is provided for the residents and undergraduate teaching is closely correlated. The excellent caliber of the men and women trained, and the work emanating from such institutions prove that the desired advancements can be made in our specialty under such administrative set ups without loss of unity. However, it functions only because of the ability, the keen insight, and the personality of the chiefs to whom these few remarks are a tribute.

The influence of the American Board of Obstetrics and Gynecology has been powerful in bringing these two fields together again. By requiring training in both, by examining in both, and by qualifying in both, acceptance of the two as one is becoming virtually unanimous.

From the very beginning the publication of specialty journals produced a common ground upon which the two could meet and unite.

The increased predominance and importance of the medical aspects, for example, endocrinology, pathology, and management of inflammatory processes, have also produced a closer bond between the two.

The specialty of obstetrics and gynecology, then, through this unity, has attained its proper place as one of the three major divisions of clinical medicine

and is on a par with the other two, medicine and surgery. Continued advancement can be accomplished by improvements in undergraduate and graduate teaching, resident training, research, and supervision of obstetric and gynecologic practice. The transmission and discussion of ideas, principles, and methods which form the basis for such accomplishments can be effected most expeditiously through the medium of specialized societies and publications. For this a large national organization is essential.

The American Gynecological Society and the American Association of Obstetricians, Gynecologists and Abdominal Surgeons reach an insufficient number of specialists because their memberships are limited. The Section of Obstetrics and Gynecology of the American Medical Association does not provide the answer, primarily because its work must be carried on under the auspices of the parent organization. It lacks independence of action as well as cohesion and permanence. The American College of Surgeons has a division of obstetrics and gynecology, but it does not adequately fulfill the needs of our specialty. This is due in part to the failure of many of our specialists to belong to the College. The College cannot establish a major division for our specialty because it has to consider the over-all picture of surgery as well as correlate the activities of numerous surgical specialties. Furthermore, here again the division of obstetrics and gynecology lacks freedom of action and solidarity of voice. It does not stand as an entity unto itself.

The first attempt to establish an organization, national in scope, which would reach the many specialists throughout the country, was made in this Central Association of ours. Such an organization was considered to be necessary for the advancement of obstetricians and gynecologists the country over, for the improvement of our specialty, and for the good of our patients. While this proposal to change the Central Association of Obstetricians and Gynecologists into a national organization was defeated, the idea was not lost. The value of the proposal was obvious and numerous proponents were acquired. The National Federation of Obstetric and Gynecologic Societies, an already existing society, was the natural group to develop the program, and, through the keen insight of its officers, the idea was consummated. As a direct result, the American Academy of Obstetrics and Gynecology has come into being and will hold its first clinical meeting in December of this year.

That this organization was needed and desired is attested to by the fact that over 4,000 applications have been received, 2,600 obstetricians and gynecologists have become Fellows in the first year of its existence, and 350 applicants are being processed at this time.

The initial and immediate objectives of the Academy have been accomplished, namely, to organize the society, to incorporate it, to acquire members, to have an annual meeting, and to promote publications and contributions.

The attainment of their remaining objectives is a subject that I wish to discuss. It is appropriate to do this at the Central Association meeting because it was here that the national organization was conceived. Furthermore, many

of you are Fellows and some are Officers and Board members of the Academy. Others who are not Fellows, but who I hope will join soon, have an interest in these remarks.

The objectives of the American Academy of Obstetrics and Gynecology can be attained best if the new organization is on the same level as the American College of Surgeons and the American College of Physicians. The objectives of these three organizations are similar. The American College of Surgeons and the American College of Physicians, since 1912 and 1915, respectively, have established for themselves the highest place in the field of surgery and medicine.

They have established precedents and customs that have proved useful to our Society. They have performed many services for the welfare of humanity and the benefit of medicine. This cannot be contested. The American College of Surgeons, for example, has been foremost in developing hospital standardizations which have elevated greatly the plane of surgery and care of the sick.

As time elapsed other organizations have come into the picture of hospital standardization and confusion, to some extent, has resulted. Accordingly, the Joint Hospital Accreditation Committee has been formed to function as a single standardization body. It is composed of representatives from the American College of Surgeons, American College of Physicians, American Medical Association, and the American Hospital Association. This Committee is worthy of support. However, one glaring defect exists in this as well as in previous standardization efforts—obstetricians and gynecologists have had too small a voice in setting hospital standards that are peculiar to obstetrics and gynecology. If our Academy were established as an American College of Obstetricians and Gynecologists it would be comparable to the American College of Surgeons and the American College of Physicians, and would accordingly have some right of representation on this new Joint Accreditation Committee. In this way we would be in a position to accomplish one of the objectives of the American Academy as now listed, namely, "To establish and maintain the highest possible standards in hospitals and practice of obstetrics and gynecology."

In some communities obstetric standards for hospitals are set selectively by state or local health authorities. Such standards may vary from those set by other organizations. A national society, at a College level, working with the Joint Accreditation Committee, could act as a guiding influence to these local governmental agencies in establishing uniform and equitable standards. Local specialized societies often lack sufficient power.

The American College of Surgeons has recognized another deficiency in surgical practice. It realizes that a surgeon, once he has passed the American Board, is no longer under supervision. It realizes that it, as a College, must take an active part in the character of surgical activities since one of its primary objectives is "to establish and maintain an association of surgeons for the benefit of humanity by advancing the ethical and competent practice of

its arts." While it has done this in the past it is making more active and extensive efforts at the present. Certainly such steps will lead to the benefit of humanity and to the advancement of surgery.

With this example before us and with the precedent the surgeons have set, we, too, can accomplish the same objectives more readily. It is an established function of a College and works at a College level. One could well anticipate that existing organizations might have difficulty in these matters because custom and precedents are lacking. The Academy at a College level could attain its objectives more easily; namely, "to establish and maintain the highest possible standards of obstetric and gynecologic practice; to perpetuate the best traditions of obstetric and gynecologic practice and ethics; and to maintain dignity and efficiency of obstetric and gynecologic practice in its relation to the public welfare." Of the four objectives listed by the Academy, three are intended *to guide the practice* of obstetrics and gynecology. This intent is apparently considered important.

A College of Obstetrics and Gynecology could better join with the American College of Surgeons, at its level and as an equal. This would strengthen the two specialties in America, give mutual support against infringement from without, and gain an objective of the Academy as it exists now, namely, "to maintain the highest possible standards for obstetric and gynecologic practice, to maintain efficiency in obstetric and gynecologic practice in its relation to public welfare."

An American College of Obstetricians and Gynecologists must stand side by side with the American College of Surgeons and the American College of Physicians in their efforts to improve medical care in this country. This can be done more efficiently as a College rather than as a division of obstetrics and gynecology within the American College of Surgeons.

While on this subject of mutual support I wish to make two points clear: First, the formation of a new College of Obstetricians and Gynecologists is not in any way an act against the American College of Surgeons; there is no grudge, no fight, no ill feeling. The new organization is proposed because I am firmly convinced that as a major branch in the field of medicine we should have our own College. In it we can advance our specialty more effectively. In the American College of Surgeons we are of necessity, and without criticism, only a minor part of all the groups with which the College of Surgeons must deal. It cannot give our specialty the major emphasis which it needs, nor can we so do, unless we have autonomy.

The second point—I am not proposing that the obstetricians and gynecologists secede from the American College of Surgeons. We must give it even more support than we have in the past. This we must do to further the aims of our own new organization. We have a task in the American College of Surgeons and we should take a full part in it. Much of the gynecology (and to a lesser extent obstetrics) in this country is done by general surgeons. These men can be reached through the American College of Surgeons, but cannot be reached through specialized gynecological organizations since such men are not eligible for membership. We must make an effort toward advancing our specialty wherever it is practiced and by whomever it is practiced.

The idea of a college is not new. England saw the advantages and in 1929 the College of Obstetricians and Gynecologists was incorporated. Later, in 1947, it received its Royal Charter and is now known as the Royal College of Obstetricians and Gynecologists. It is on an even plane with the Royal College of Surgeons founded in 1800, and the Royal College of Physicians founded in 1518. In their country, as in ours, the formation of the College of Obstetricians and Gynecologists followed the inauguration of the other two Colleges by many years. This is understandable because of the strong tradition and the slow evolution that are necessary to the solid formation of any medical specialty.

Since the formation of the Royal College of Obstetricians and Gynecologists, obstetrics in England has improved tremendously and the influence of the College has been felt throughout the entire Empire. Only as a College were they able to carry out their objectives. The Royal College of Obstetricians and Gynecologists has played a large part in uniting, under one fold, the obstetricians and gynecologists of England. In discussing the Royal Colleges of England, I cannot help but refer to the remark of Franklin Martin[4] at a conference in Washington: "This Committee has met here to consider the advisability or inadvisability of organizing an American association that would parallel the Royal College of Surgeons." From that conference the American College of Surgeons did evolve and did become the parallel organization to the Royal College of Surgeons. What is being proposed is that an American College of Obstetricians and Gynecologists be established which would be parallel to the Royal College of Obstetricians and Gynecologists—a similar objective to that of the group which started the American College of Surgeons.

In England, the Charter of the Royal College of Obstetricians and Gynecologists stands out as a beacon to light up the fact that obstetrics and gyneclogy has reached its natural and mature position as one of the three major divisions of medicine. In our country obstetrics and gynecology holds a similar place. It should likewise be dignified by the establishment of an American College of Obstetricians and Gynecologists.

The American Academy of Obstetricians and Gynecologists could be transformed into the College simply by changing its name and act of incorporation. With the support of all of us, with the prestige that the title College carries with it, and with the precedents and customs already established by such organizations we, as a College, could do the maximum toward establishing and maintaining high standards, perpetuating the best traditions and ethics of practice, and maintaining efficiency of practice in its relationship to public welfare.

It is, therefore, proposed that the American Academy, a logically planned and firmly founded Society, become the American College of Obstetricians and Gynecologists.

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THE PHYSICIAN IN CURRENT FICTION*

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A CERTAIN occupational hazard confronts any man who, over a period of years, has addressed his colleagues on strictly professional subjects. He is unsettled by the suspicion that what he is about to say he has said before, and that his audience may resent his warmed-over remarks. Therefore, I shall remove the hazard of repetition by turning to a subject that is new to me and, mercifully, may be new to some of you. I invite you to step with me outside the charmed circle of surgical techniques, laboratory procedures, statistical analyses, and mutual admiration—to step out of our professional skins, as it were, and look coolly upon the body medical, as the rest of the world is doing increasingly these days.

All of you recall Robert Burns's famous wish as he eyed the louse upon the most fashionable and self-righteous bonnet in church:

> O wad some power the giftie gie us
> To see oursels as others see us!

I hesitate to make invidious comparisons, but it is just possible that the dignity of our professional posture may be somewhat impaired by the presence of allegorical lice. It would be well for us to know, for the eyes of others are upon us. What those eyes make of us *individually* we may never know. As a *profession,* however, we have sat for a full-length portrait to our men and women of letters. Through the power of the novelist we can sit in the audience and literally see ourselves as others see us.

We cannot expect the fictional portrait of ourselves to be flattering; the style in portraiture today is candid. We may, however, expect the portrait to be fair because of the presence of physicians in the field of writers—men like Frank Slaughter in our own country, and A. J. Cronin and Francis Brett Young in England. It would be an impertinence for us to like or dislike what they have made of us, since we have been their models, and since the resultant portrait is, for better or worse, the composite image which irrevocably represents us in the lay mind.

Certainly we have no cause to complain of neglect. The physician has occupied an increasingly prominent place in the literary portrait gallery. It may even be argued—safely, I hope, in the bosom of the family—that he has become the most fascinating figure in fiction, the one character who can be counted upon to provide salable stimulus to all segments of the reading public. Master of the controllable forces of life and death, the doctor is the closest human approach to deity, and as such has the maximal dramatic potential as either hero or villain. The physician into whose hands a life is committed is

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an object of faith terrifying in its totality. Because his work confers upon him a power unique in human society, his intimate private life becomes almost as compelling a public interest as that of a king, a movie star, or even a presidential candidate. The work itself not only confers the power, but provides the appeal of lurid ethical conflict plus the inevitable morbid thrill of blood, pain, and imminent death. It is also highly technical and contains the thrill of the esoteric; every operation is to the layman a trip to Mars. The very language of medicine hypnotizes him with its heady poetry. Precisely when he least understands it, it most titillates his imagination. But, in the end, the power is the thing that holds him fast. The elemental drama of life revolves about the quest for power and the abuse of power, and the doctor is called and recalled into the literary arena by the tireless curiosity of his public to learn and to judge how he acquires and dispenses his unique power.

The influence of our literary image upon the public mind is a continuing thing. The specifications of the medical drama may change with the times, as portraits in a family gallery date themselves by the cut of collars and whiskers without destroying the lineal resemblance. Forty years ago a little volume called *Red Pepper Burns* instilled in me a state of compulsive hero worship. Nothing could be finer, it seemed to me, than to be like this truculent, kindly, brilliant man, who ministered to his community with high-handed devotion and a magnificent, high-powered gas buggy which he called the "Green Imp." How merely quaint Dr. Burns and his little world might seem today, I am not too anxious to discover. They had then sufficient vitality to send at least one starry-eyed boy into the field of medicine, and I like to think that the virtues and challenges that inspired me then were of somewhat more enduring design than the "Green Imp." But the times will be served. The country doctor, the family practitioner, has given way, in fiction as in life, to the specialist. The hero of the modern medical novel is often required to pass through a period of general practice as a kind of purgatory, to free him of callowness and arrogance, and to teach him something of patience, humility, and human values. He rarely remains there. Luke Serocold, created by Helen Ashton more than twenty years ago, was almost the last of the great country doctors in fiction. A few years later, James Gould Cozzens effectively poisoned the strain of the general practitioner with his quietly devastating portrait of George Bull in *The Last Adam.*

The new medical hero is a scientist. His ambition runs to narrowing his field of work to the point of mastery. The pattern is set by the two most famous physicians in modern fiction: Sinclair Lewis' Martin Arrowsmith, and Andrew Manson, hero of Cronin's *The Citadel.* Oddly enough, the specialty of neither of these celebrated figures is quite typical. Arrowsmith was a bacteriologist, Manson a chest man. A smattering of other specialties appears as well—here an orthopedist, there a radiologist, and, in at least one case, a gynecologist. On the whole, I am afraid that the writers of medical fiction have not viewed gynecology and obstetrics as heroic branches of the profession, a fact which would be much less disturbing were we not so popular a choice for villain. The medical hero of today, replacing the country doctor of yesterday, tends to be

a surgeon—frequently, and perhaps predictably, a neurosurgeon. Nowhere are technology and the drama of survival so electrically conjoined as in the operating room. Of all the implements of civilization, man stands most in awe of the scalpel. Of all physicians the surgeon is most godlike in his powers; of all surgeons, the neurosurgeon. No one has understood this better than Lloyd Douglas, who has twice selected a neurosurgeon to embody his thesis of the combined power of medicine and religion.

Whatever his specialty, the medical hero has a more or less standard personality and career which serve as a framework to the author for his basic impressions of the genus medicus. We see him first as a student struggling through the incredible difficulties of freshman anatomy and physiology. His difficulties frequently are compounded by poverty and social obscurity, and by a brilliance of mind that is not always correctly understood. He has a rude and uncultivated charm, is generally untidy, painfully sincere, frequently discourteous. In spite of these qualities, he attracts and ultimately wins a nurse, a debutante, or even both. He has all the current virtues and no disabling vices. While his buddies are sowing their sexual and alcoholic wild oats, he is sublimating these drives in study and a firm bite on a newly acquired pipe. A demon for work, he has no time for parties, and spends much extra time in the laboratory pursuing his favorite subject. Here he is discovered by a world-renowned professor who promptly makes him his assistant. This soaring career always culminates in first honors at graduation.

After the neophyte graduates, the novelist has a choice, so far apparently denied him by the rigid pattern of medical heroics: the young doctor may, on completion of his internship, become a resident in a specialty on the staff of his alma mater; or, under economic compulsion, reluctantly he may turn down opportunities for further study and strike out to open practice on his own or become junior member of a less distinguished medical group. Also optional is marriage, there being about equal dramatic potential in celibacy under fire and the conflict between domestic and professional allegiances. In any case our hero is a dedicated man, dedicated to the practice of medicine by the strict spirit of the Hippocratic oath.

The man thus dedicated is a titan of sorts. He has his human frailties, but he doggedly suppresses them, even at the expense of personal happiness, to pursue his duty as a physician to the limit of his vitality. The authors of fiction cram into the compass of three or four hundred pages an accumulation of professional tribulations scarcely to be sustained by flesh and blood. The favorite device for exhibiting the devotion and endurance of the doctor is the epidemic. Typhoid is favored about two to one, though influenza and diphtheria have served well and repeatedly, and even the plague, as readers of *Arrowsmith* will recall.

The most obvious quality about such a figure is his enormous stamina. Most authors share a grotesque compulsion to make of the doctor, whatever else he may be, the most harried man in the world. A case in point is Mary Roberts Rinehart's omnibus medical novel, *The Doctor*. Its theme is "We are not gods but men," yet the story loads the hero with the labors and responsibilities of a

god, while limiting him to the judgment of a ten-year-old boy. He works nonstop through not one but two typhoid epidemics; wages a one-man war on the tycoon whose negligence is responsible; gives up the right girl on principle, marries the wrong girl to keep her off the streets; assumes the burden of his rival's illegitimate child; goes through the war in one long waking nightmare of mud, blood, and gangrene; attends patient after patient with haggard, round-the-clock bedside vigils; operates under impossible conditions to the point of collapse; finally suffers injury to the radial nerve, from which he recovers by a prodigious effort of will just in time to perform an emergency appendectomy. For sheer Olympian stamina Chris Arden leads the field.

Another prominent characteristic of the medical hero is the coolness with which he applies his phenomenal skill in the most appalling emergencies. Every popular novelist sees in the doctor the modern knight, thrown from time to time into unequal but always victorious combat with the dragon of sudden death. A useful emergency for vivid effect is tracheotomy performed on an underprivileged child already cyanotic from advanced diphtheria. Alan Hart's Dr. Mallory gets his surgical baptism with such a case. Ran Warren, too, and Brett Young's Jonathan Dakers successfully perform the operation under the most adverse conditions with acrobatic dexterity. A difficult delivery, too, has much of this touch-and-go appeal, and the literary doctor tends to be a spectacular amateur accoucheur. Warren and Manson are typical of the audacious but inexperienced young practitioners whose struggle to preserve one life is suddenly multiplied into a struggle to preserve two, with the attendant confusion of Pituitrin and massage here, Adrenalin and massage there, here an injection of saline, there a little artificial respiration, and in the end the double reward of a steadying maternal pulse and a lusty wail to bear witness that a good doctor is a very great man indeed.

The hero of medical fiction is impressive for the depth of his physical courage. Every shade and variety of sinner is represented in the gallery of literary physicians, but I can remember no physical cowards among them. Indeed, the poorest of them takes in his stride the routine hazards that appall the layman, and the best of them stands habitually and knowingly a pinprick from death.

Even more significant than his physical courage is the moral courage of the doctor in fiction. The plot of the medical novel is largely an instrument to demonstrate that the good doctor would rather be right than rich. Too often, in the pages of fiction, drama, if not truth, dictates that he cannot be both.

Invariably, the reader finds, the good doctor is a crusader. He is a crusader for better health in his community; his opposition, by an irony familiar to us all, is supplied by the community itself. The best people in town are involved in the practices and conditions which he wishes to reform. Typical is the experience of Dr. Tony McNeill, characterized in the title of Elizabeth Seifert's novel, *Young Dr. Galahad.* Tony wants to rid his town of a dangerous old midwife-abortionist, but she pays protection and performs valuable services for the best families with admirable discretion. He wants to institute routine Wassermanns

in the obstetrical department of the hospital, but the test is an insufficient respecter of social position; to persevere is to court ostracism and failure. Against such problems the medical profession is seen to stand—but not united.

The saddest fact in the world of medical fiction is that the good physician is opposed most of all by indifference, venality, incompetence, and malice within the profession itself. In books, our hero stands pretty much alone. Oh, he picks up a similarly dedicated comrade now and then, but the ugly truth is that the good doctor is much more likely to be pictured as the exception than as the rule. The villains are multiplied but are not invented. We may quarrel with the author as to how many bad doctors there are, but not as to how many kinds of bad doctors there are. Let me point out a few of the well-modeled skeletons which our medical novelists have been rattling for the edification of the public.

First we have what many have made of that once hallowed figure, the general practitioner: a fine old fellow in his way, but unambitious and simply not up to the demands of an increasingly difficult job. Old Doc Fetterbaum in *Disputed Passage* exhibited the instincts and activities of a philanthropist, but he couldn't be troubled to keep current in medical progress, even though "people died who shouldn't." He was a kind man, Douglas remarks with quiet penetration, "who went about doing good up to the very point of performing the real job he claimed as his vocation." George Bull, the misguided and lazy practitioner of Cozzens' *The Last Adam,* was a cynic and a gambler on probabilities. In his opinion ninety-five per cent of patients get well or die irrespective of medical attention, and the effort to identify and treat the remaining five per cent is distinctly disproportionate. An occasional ruptured appendix or eclampsia means nothing to such a man, who believes, or at least rationalizes, that you can't test everybody for everything.

More formidable bunglers are the politically entrenched practitioners against whose slipshod and often criminal methods the hero opposes himself with an impotent fury. Many of them, I regret to say, are what novelists like to refer to as "fashionable" gynecologists. For instance, young Dr. Galahad's *bête noir* is a gentleman so overconfident that he cannot be troubled with microscopic examination of curettings and thus permits the avoidable development of advanced carcinoma. The gynecologist-hero of *Eve's Doctor* complains bitterly (and fruitlessly) that his unscrupulous colleague, Dr. Carrick, cannot distinguish pregnancy from tumor and that he has killed or maimed more women than Jack the Ripper. His special dereliction is the premature use of forceps, in which his only virtue is that of perseverance.

Often the doctor's villainy lies not so much in incompetence as in unscrupulousness. There are many ways of making an easy dollar in medicine, all of them contrary to the notions of Hippocrates, all of them known with intimate relish to the writers who interpret us to our public. It is the pious contention of some of these writers that wealth and honesty are incompatible in a physician, a thesis developed in its most homiletic form by one of our own number, Dr. Cronin, in that fabulously profitable sermon, *The Citadel.* Dr. Brett Young, too, has given the world a model of the unscrupulous surgeon in the person of Dr. Craig in *My Brother Jonathan.* Craig made appendicitis a

fashion in his town and, when that began to pall, had the ingenuity to discover first the gall bladder and then (masterpiece of restraint) hospitalization for "observation." Our own specialty has been singled out for peculiar opprobrium. There is hardly a medical novel that does not have its abortionist operating discreetly behind the veneer of professional respectability. But the most villainous obstetrician of all is Frank Slaughter's Dr. Sarnov, who, while not guilty of gross illegality in his practice, is not above using his patients to augment his income. It is a coincidence far happier for Sarnov than for his victims that cesarean sections, for which he charges five times as much as for normal deliveries, occur ten times as often on his service as in other comparable hospitals.

In another category of medical villains is the cold statistician. Happily, constructive research and publication are not, like the comfortable bank account, a standard symptom of professional corruption. But the mere compiler of data, the pseudo scientist to whom figures speak more loudly than voices, is suspect and the case against him is documented by many persuasive instances. "The course of epidemics," writes John Stuart Arey, "is a source of great satisfaction to statisticians." In *There Was No Yesterday* he uses the classic typhoid epidemic to dramatize the contrast between the practical humanitarian and the public health officer whose chief object is personal recognition by publication rather than the conquest of disease. A statistically minded surgeon in *Hope Deferred* has a ward full of patients in various stages of unfinished surgery. When an enterprising assistant performs a radical operation in the hope of accomplishing something definitive, the older man spells out the shabby truth behind his conservatism by saying, "Damn you! You know he'll die and add to our mortality rate!"

It is the fate of the average medical hero in fiction to be cursed and balked at every turn by those who are bent with inscrutable perversity upon thwarting the progress of medical science. And so the battle lines are drawn, the worthy physicians, a small but determined force, against the ubiquitous worshippers of expediency. There is a standard scene, at once stirring and preposterous, in which the hero, hounded before some august tribunal for allegedly unprofessional acts, turns at bay and utters a cathartic blast of denunciation. In the end, however, right is triumphant; our hero is invariably vindicated.

Perhaps, in final analysis, the chief distinction of the good doctor, as conceived by the novelist, is his conscious pride in his calling; not that he is free from error or the thousand frailties that flesh is heir to, but that he is free from all confusion as to what he is doing in the medical profession. Like Elizabeth Seifert's Dr. Mallory, "he thinks about medicine the way missionaries are supposed to think about their work: it's not a way to make a living but a way to live." He has at least one feature in common with Red Pepper Burns and his other forebears of the horse-and-buggy era, a certain idealism, which he and they and we are rather embarrassed to discuss. Novelists, however, are not embarrassed to discuss anything, even when the discussion degenerates into the mawkish sentimentality to which idealism is so unhappily prone. We cannot ignore the hero's repeated stand on two important issues in modern practice.

The first of these is political. The physician of contemporary fiction is vigorously dissatisfied with the present distribution of medical care. He feels that the profession and the public are joint victims of economic maladjustments. Altogether, our heroes take a wide variety of positions on this vital and prickly issue, but they do take some position, other than that of the ostrich.

The other issue in which the medical hero's idealism involves him is philosophical and is embodied in a question asked by one of Michael Murrough's patients, "Is a patient a person, or merely the shell of a more or less interesting tumor?" According to Murrough, "every good doctor knows that there are no diseases—only persons having diseases," but the writers of fiction have made this the most difficult and dramatic lesson the doctor has to learn. In novel after novel the contrast is drawn between the priests and the plumbers of the profession.

It is not as a mere technician that the doctor earns his high regard, but as a man among men. There is something timeless about the tribute paid by Robert Louis Stevenson to the physicians who had attended him in his almost constant ill health: "There are men and classes of men that stand above the common herd . . . the physician almost as a rule. He is the flower (such as it is) of our civilization; and when that stage of man is done with, and only remembered to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race. Generosity he has, such as is possible to those who practice an art, never to those who drive a trade; discretion, tested by a hundred secrets; tact, tried in a thousand embarrassments; and what are more important, Herculean cheerfulness and courage. So it is that he brings air and cheer into the sick-room, and often enough, though not so often as he wishes, brings healing."

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807 Spruce Street

AN EXPECTANT MOTHER'S PRAYER*

JOSEPH E. KOPCHA, B.S., M.D., F.A.C.S., GARY, IND.

DR. KIMBROUGH'S remarks yesterday brought back to light some of the things we do in our offices daily, and more or less shrug off our shoulders, but I have not seen a man yet—either in this group or in these United States—who did not particularly like a little praise, a little pat on the back. One of my patients, two weeks ago, gave me this little prayer which she wrote. I thought the audience would like to hear a prayer for the maternity doctor.

"O Lord, Jesus Christ, Lover of little children, grant your abundant blessings to my doctor. If there is any task more important than the preserving of life, it is the task of bringing that life into the world.

"Give my doctor a deep appreciation of the work that he performs. May he ever know how precious that work is in Your sight. Guide his hand at all times in his work, and may it never do a work to Your dishonor.

"May he ever regard his office as a sacred trust, received from You. And finally, may he one day know Your rich rewards for having striven earnestly and faithfully to 'suffer the little children' to come unto You, according to Your ardent desires. Amen."

These are the little Adrenalin injections that make us work day and night, that get us out of bed at 3 in the morning.

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*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

STUDIES ON FETAL MEMBRANES*

I. Bursting Tension

D. N. DANFORTH, PH.D., M.D., THOMAS W. MCELIN, M.D., M.S., AND M. N. STATES, PH.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, and the Evanston Hospital, Evanson, Ill., and from the Chicago Branch of the Office of Naval Research)

PREMATURITY is now recognized as the most important cause of neonatal death. In 31 per cent of a recent series of premature births, spontaneous rupture of the membranes preceded the onset of labor by hours or days.[1] In such cases, weakness of the membranes themselves is often indicated as the precipitating cause of this accident, the presumption being that had the membranes been stronger the pregnancy might have continued to term. Because of this rather common clinical opinion, it seemed desirable to study the fetal membranes in an attempt to determine whether their varied clinical behavior might be explained by variations in their basic structure. To our knowledge, such an approach to this problem has not been made. Accordingly, a series of studies was undertaken with this purpose. The first of these, reported herewith, was made in an effort to determine whether it might be possible to correlate clinical behavior with strength of the membranes, as evidenced by their ability to withstand pressure.

Materials and Methods

Intact placentas with membranes attached were obtained immediately after delivery. The membranes were carefully trimmed away from the placenta, and were immersed in normal saline for a period varying from 5 to 20 minutes. They were then placed upon a clean, moistened towel, and carefully arranged in such a manner as to form a solid sheet. Particular care was taken not to injure the membranes, or to separate the chorion from the amnion. Samples about 5 cm. square were then cut and returned to the normal saline, being removed one by one for testing.

The testing apparatus consisted of a mercury manometer 1 M. high, filled with mercury to the 50 cm. mark. One limb of the manometer was connected by rubber tubing to a T tube. One limb of the T tube was connected through a special cutoff valve to an ordinary oxygen tank; the cutoff valve was of a type which allowed the escape of small amounts of oxygen under precise control. The remaining limb of the T tube was connected by a segment of rubber tubing to a 3-inch piece of 5/16-inch glass tubing with rounded end and a depression to allow tying. One of the 5 cm. squares of membranes was then loosely placed over the end of the glass tubing, chorion down, and firmly tied in place with an umbilical cord tape. This material was used since its flat surface minimized the possibility of injury to the membranes in securing them to

*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

the tube. Oxygen was then introduced into the system, its pressure being distributed equally against the membranes and against the mercury in the manometer. This resulted in the formation of a "bubble" of membranes, which gradually increased in size until it burst. By increasing the pressure very slowly, it was possible to read accurately the pressure which was attained at the time of rupture. In most cases, rupture of the bubble occurred at some point on its spherical surface remote from the tie tape. Occasionally, rupture occurred at the point where the membranes were tied to the glass tubing; these were discarded since it was presumed that the membranes had been injured by tying.

Each membrane studied was numbered, and data were recorded concerning the dilatation of the cervix at the time of rupture, the manner of rupture of the membranes (whether spontaneous or artificial), the age and parity of the patient, and the duration of pregnancy at the time of rupture of the membranes. The data obtained employing the above apparatus are divided into two groups.

Group I consisted of 89 cases in which only the pressure required to burst the membranes was recorded. Two samples of each membrane were tested.

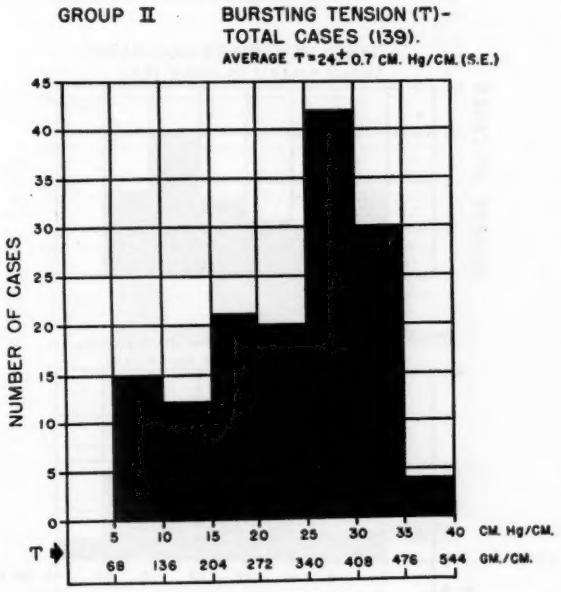

Fig. 1.

Group II consisted of 139 cases, in each of which from 3 to 5 separate readings were made. In addition to the bursting pressure, the diameter of the bubble at the time of bursting was also measured. For this latter purpose, a template consisting of half circles of gradually increasing diameters was held immediately in front of the expanding sphere of membranes, being moved to patterns of greater size by 0.1 cm. stages as the sphere enlarged. By inflating the membranes very slowly, it was quite easy to follow the increasing diameters. As most of the membranes ruptured within a range of certain rather common diameters, it was not difficult to obtain an eye level "top of the meniscus" reading of the manometer, and at the same time keep the template attuned to diameter changes of the bubble. The above data for each sample of membranes were substituted in Laplace's formula for a hollow sphere ($P = 2T/r$, where P = pressure in centimeters of mercury per square centimeter, r = radius in centimeters, and T = tension in centimeters of mercury per centimeter). By

applying this formula, it is possible to obtain the tension (T) in the bubble wall at the time of rupture. We have referred to this value as the *bursting tension.*

The coefficient of variation was computed in order to note the consistency of the several determinations on individual membranes. An arithmetical average T of all determinations on any one membrane was computed, and employed in the subsequent correlations.

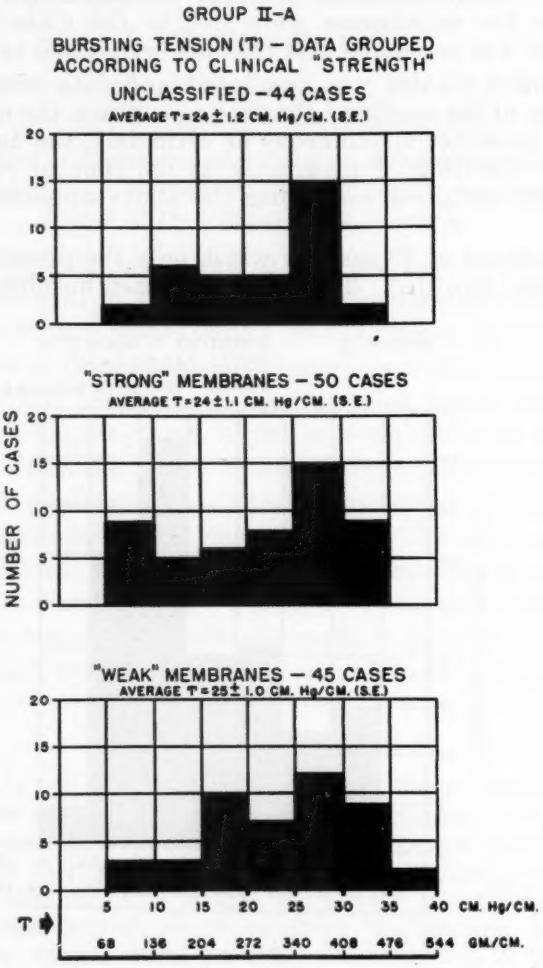
GROUP II-A
BURSTING TENSION (T) – DATA GROUPED ACCORDING TO CLINICAL "STRENGTH"
UNCLASSIFIED – 44 CASES
AVERAGE T = 24 ± 1.2 CM. Hg/CM. (S.E.)
"STRONG" MEMBRANES – 50 CASES
AVERAGE T = 24 ± 1.1 CM. Hg/CM. (S.E.)
NUMBER OF CASES
"WEAK" MEMBRANES – 45 CASES
AVERAGE T = 25 ± 1.0 CM. Hg/CM. (S.E.)
0
5
10
15
20
T
5 10 15 20 25 30 35 40 CM. Hg/CM.
68 136 204 272 340 408 476 544 GM/CM.

Fig. 2.

The mean T values were grouped and studied according to the following factors:

A. Clinical strength of the membranes.
B. Duration of pregnancy at the time of rupture of the membranes.
C. Age of the patient.
D. Parity.

Statistical significance for each of the various subgroups under the above headings was determined by standard error, and frequency distribution curves were plotted.

In addition to the above, a third group of data was obtained (*Group III*). This consisted of 44 additional cases in which the thickness of the relaxed membranes was determined, at 5 different sites for each membrane. The in-

strument employed for this purpose was a micrometer caliper equipped with a sensitive ratchet release which permitted the application of uniform pressure for each determination. The modal value of these readings was regarded as the representative thickness of the specimen under consideration. These data were correlated with clinical strength of the membranes.

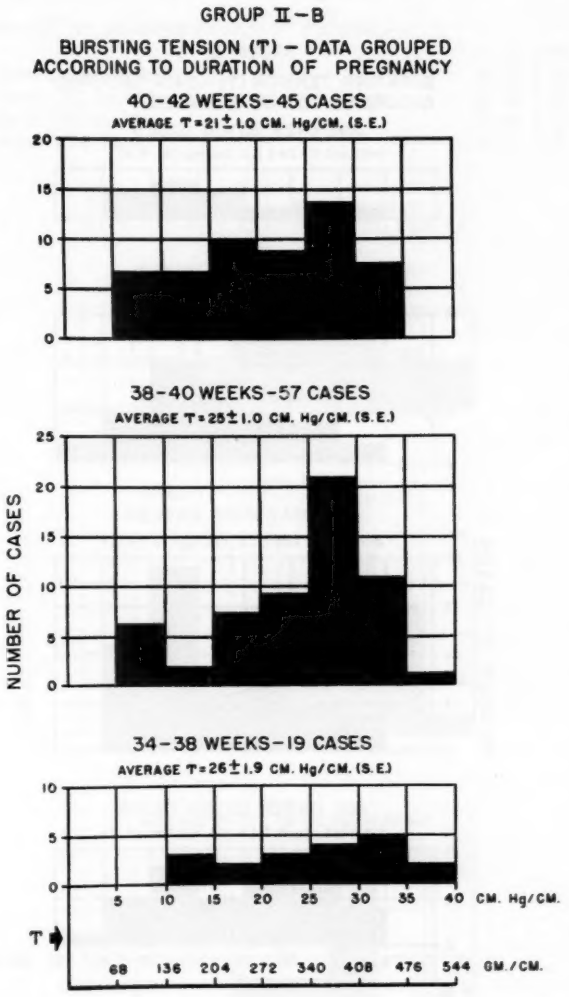

Fig. 3.

Results

Group I.—Since the diameter of the bubble of membranes was not recorded in the 89 cases in this group, all of the data were discarded as being without significance. It is apparent from Laplace's formula that for a given pressure the tension in the wall of a hollow sphere increases with the radius, and that the smaller the sphere the higher the pressure it will withstand. This principle has been recently utilized in studying the hemodynamics of aneurysmal sacculation,[2] and the relation of intestinal intralumen pressure to wall tension.[3] Accordingly, the only result obtained from this group of cases was the acquisition of a high skill in handling the membranes, securing them to the measuring device, and making the other manipulations required for the deter-

mination of bursting pressure. Hence, the fact that these estimations were made is recorded here, and a certain salvage accrued from this effort.

Group II.—For the 139 membranes of this group, the coefficient of variation was found to be 19 per cent. Although this value is high, variance analysis studies show that even with this consistency variation in any one membrane, the method is sufficiently precise to allow detection of differences between membranes.

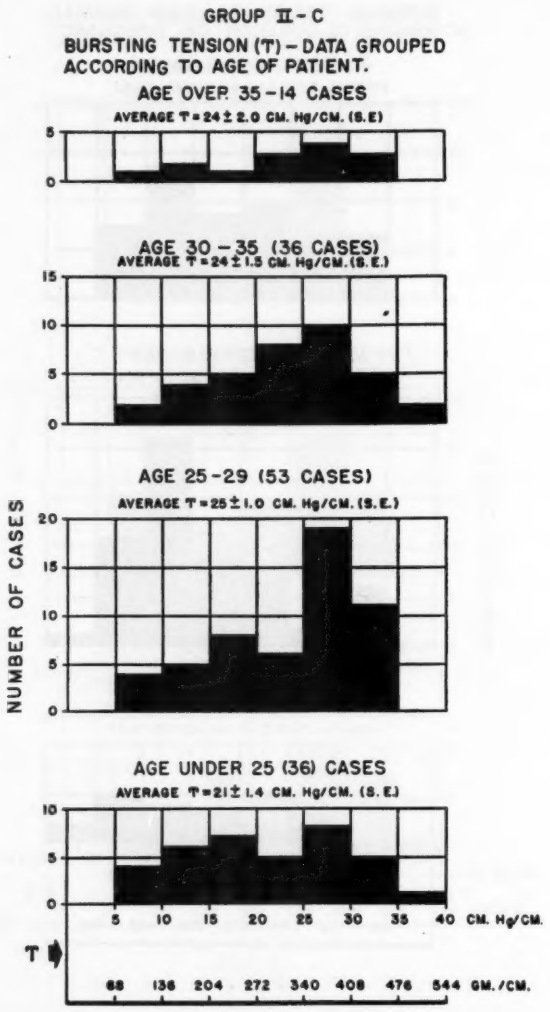

Fig. 4.

The average bursting tension in 139 membranes was 24 cm. Hg/cm. ± 0.7 (S. E.).

A. Bursting Tension (T) in Relation to Clinical Strength of the Membranes.—

	AV. T (CM. HG/CM.)
"Weak" membranes—those ruptured spontaneously before 3 cm. dilatation (45 cases)	25 ± 1.0 (S. E.)
"Strong" membranes—those ruptured spontaneously or artificially after 8 cm. dilatation (50 cases)	24 ± 1.1 (S. E.)
Unclassified membranes—those ruptured artificially in early labor or for elective induction of labor, or cesarean section (44 cases)	24 ± 1.2 (S. E.)

B. Bursting Tension (T) in Relation to Duration of Pregnancy.—

		AV. T (CM. HG/CM.)
40-42 weeks (45 cases)		21 ± 1.0 (S. E.)
38-40 weeks (57 cases)		25 ± 1.0 (S. E.)
34-38 weeks (19 cases)		26 ± 1.9 (S. E.)
1 case at 29 weeks:	T = 23 cm. Hg/cm.	
1 case at 29 weeks:	T = 13 cm. Hg/cm.	
1 case at 27⅞ weeks:	T = 36 cm. Hg/cm.	

C. Bursting Tension (T) in Relation to Age of Patient.—

	AV. T (CM. HG/CM.)
Age under 25 years (36 cases)	21 ± 1.4 (S. E.)
Age 25 to 29 years (53 cases)	25 ± 1.0 (S. E.)
Age 30 to 35 years (36 cases)	24 ± 1.5 (S. E.)
Age over 35 years (14 cases)	24 ± 2.0 (S. E.)

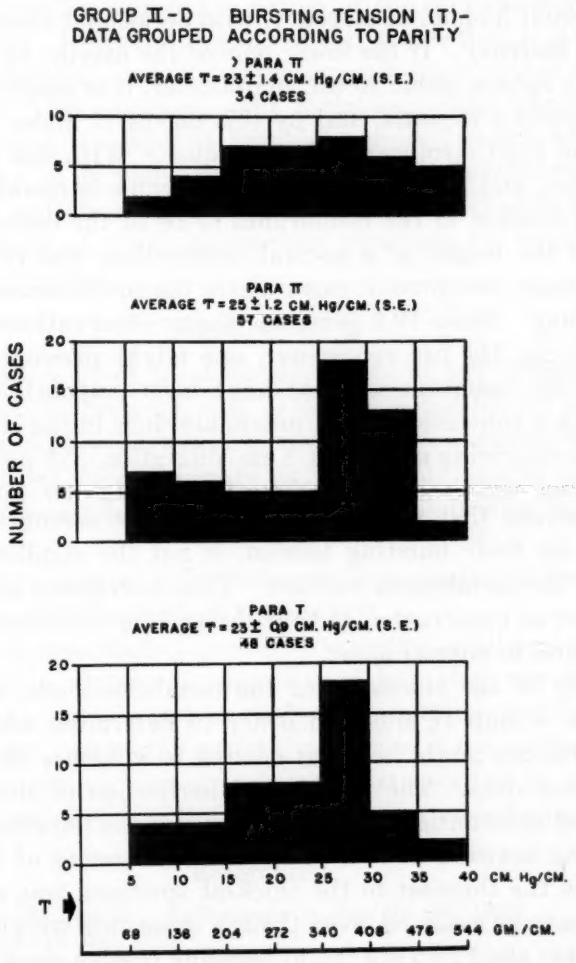

Fig. 5.

D. Bursting Tension (T) in Relation to Parity.—

	AV. T (CM. HG/CM.)
Para i (48 cases)	23 ± 0.9 (S. E.)
Para ii (57 cases)	25 ± 1.2 (S. E.)
More than para ii (34 cases)	23 ± 1.4 (S. E.)

The frequency distribution of all the data in Group II is shown in Fig. 1, and for the various subcategories, in Figs. 2, 3, 4, and 5. All the curves showed

a similarity of pattern, the modal frequency being at a tension between 25 and 30 cm. Hg/cm. in all cases except those from 34 to 38 weeks, where it fell between 30 and 35.

Group III. Thickness of the Membranes.—
Average thickness (44 cases) 214 $\mu \pm 6.1$ (S. E.)
Membranes ruptured spontaneously or artificially after 8 cm. (17 cases)
Average thickness, 230 ± 14.3 μ
Membranes ruptured spontaneously before 3 cm. (9 cases)
Average thickness, 213 ± 8.5 μ

Comment

Caldeyro and associates[4] have found the intrauterine pressure in normal labor to be about 35 mm. of mercury, with occasional observations of the order of 50 mm. of mercury. If the lower pole of the uterine cavity be considered as a portion of a sphere about 10 cm. in diameter, it is possible to substitute these values in Laplace's formula, and by this means to make an estimation of the tension in the fetal membranes during labor. With due consideration of the many variables, and awareness that such a value is merely an approximation, one finds the tension in the membranes to be of the order of 8.75 cm. Hg per centimeter at the height of a normal contraction, and 12.5 cm. Hg per centimeter in the more exceptional cases where the intrauterine pressure reaches 50 mm. of mercury. Since 19.4 per cent of our observations of bursting tension are below 15 cm. Hg per centimeter, one might presume that in these cases weakness of the membranes could have been responsible for their rupture. However, such a conclusion seems untenable since in the clinically strong membranes (those rupturing only after 8 cm. dilatation), 28 per cent of all readings showed bursting tensions of less than 15 cm. Hg per centimeter. One may therefore, conclude that the inherent weakness or strength of the membranes, as evidenced by their bursting tension, is not the significant factor in determining when the membranes rupture. This correlation also suggests that the membranes are so constructed as to withstand intrauterine pressures which exceed those found in normal labor.

Our study of the thickness of the membranes was made after the conclusion of the Group II study in order to determine whether the spread of these measurements might be great enough to influence the distribution of the bursting tension data. The frequency distribution of the thickness measurements followed substantially the same curve as the bursting tension, the modal thickness being between 228 and 254 μ with extremes of 152 and 330 μ. The variation from the thinnest to the thickest specimen was about 2 times. Consequently, it may be assumed, even though these data were taken from different membranes, that the 1 to 7 spread in bursting tension shown in Group II would be much reduced if thickness were taken into account. It is desirable that such data be correlated in the same membranes with bursting tension and with the clinical data presented here.

Since approximately half of all neonatal deaths are due to prematurity, it is evident that any significant contribution to our knowledge of any of the causes of premature labor is of enormous importance. If the cause of prema-

ture rupture of the membranes were known, and could be eliminated, it might be possible to reduce the incidence of prematurity by as much as 30 per cent. Despite the urgency of this problem, virtually no definitive work has been directed toward its solution. Although the membranes themselves appear to be the logical point of departure for such studies, the standard textbooks and the obvious literature contain no useful information regarding this structure. The present preliminary study tends to focus our attention away from the concept that physical strength or weakness of the membranes might be the responsible factor in premature rupture. The possibility now arises that extraneous factors, unrelated to the inherent strength of the membranes, may be the causative item. Local weakening or dissolution of the membranes at the point where they overly the internal os, due to the action of the cervical secretions, is not an unlikely possibility. However, in spite of this suggestion, it is essential that further studies be directed toward completing our information regarding the precise nature of the fetal envelope. The initial reasoning which directed our thoughts to the clinical concept of "tough" versus "weak" membranes has expanded and become, to us, increasingly provocative. It is therefore desirable that other physical and chemical properties of the fetal membranes be determined, and the details of their microscopic structure be established. Such studies are now in progress.

Conclusions

1. Bursting tension gives a reasonable index of the ability of the fetal membranes to withstand pressure, and is therefore considered to be of use in determining the inherent weakness or strength of the membranes.

2. Premature spontaneous rupture of the membranes is apparently not due to the inherent weakness or strength of the membranes, as evidenced by their bursting tension.

3. The bursting tension of the membranes is unrelated to the age or parity of the patient, or to the duration of pregnancy.

4. The frequency distribution curves of bursting tension of the fetal membranes assume uniform patterns irrespective of how they are grouped. They appear relatively the same whether studied in relation to clinical strength, duration of pregnancy, age of the patient, or parity of the patient.

5. The fetal membranes appear to be so constructed as to withstand pressures which exceed those due to the uterine contractions of normal labor.

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Discussion

DR. W. C. KEETEL, Iowa City, Iowa.—It is gratifying to see scientific investigation of the problem of premature delivery turning to factors other than nutrition and maternal disease complications. Clinically, the membranes are most important in obstetrics. They

form a barrier against infection. When they are ruptured, uterine contractions are often inaugurated or increased. The older clinicians thought that the membranes were very important in forming a dilating wedge, and that "dry labor" often resulted in prolonged and difficult labor, cervical tears, and an increased incidence of intracranial hemorrhage. It has been shown that this is not true, and now it is felt that the most effectual method of inducing labor is by the artificial rupture of the membranes. A recent study of prolonged labor conducted in the Department of Obstetrics and Gynecology at the State University of Iowa Hospitals revealed that the onset of labor was spontaneous, and the membranes remained intact for many hours in 55 per cent of the series.

After the rupture of the membranes, in over 50 per cent of the cases, the cervix was completely dilated within 2 to 3 hours, despite the fact that many of these patients had been in labor 30 to 40 hours, and had achieved a cervical dilatation of only 4 to 5 cm. We all have seen problems of prolonged second stage solved by simple rupture of the membranes. In both these instances one may ask are the membranes abnormally strong.

The experiment conducted by Dr. Danforth has shown that the strength of the membranes as evidenced by their bursting tension is rather uniform. He has also pointed out that the greater the area of membranes the greater the tension produced by a given pressure. This may be illustrated by Fig. 1. The curve in the upper corner shows how the tension on the membranes builds up as the surface area (cervical dilatation) increases even though there is no increase in pressure per unit area. As a crude illustration note the lines on the chart with unit weights in each unit of length. Obviously, the tension at the ends builds up as the line increases in length. The lower diagram shows unit weights on each unit of surface area, again the tension builds up at the periphery even though the pressure per unit area is not increased.

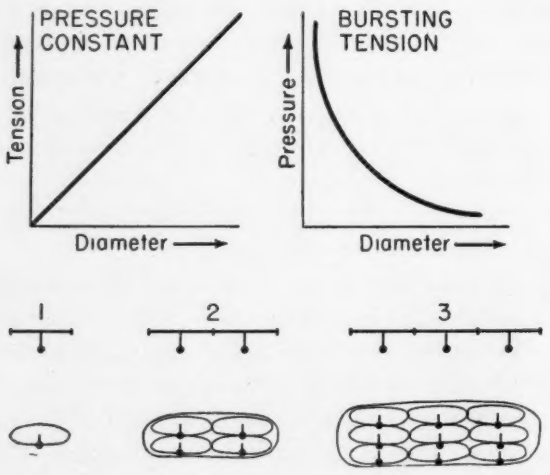

Fig. 1.

This shows why the "bursting tension" of the membranes would be reached at a lower pressure as the cervix dilated. The upper figure shows the bursting tension at lower pressure with larger diameters. This could account for certain spontaneous premature ruptures of the membranes if the cervix was dilated. It is obvious that the strength of the uterine contractions and the degree of cervical dilatation must be considered simultaneously.

These observations and calculations assume that the membranes are bulging freely into space without any support. Actually the membranes bulge through the cervix and are supported by the vaginal wall and the pelvic diaphragm. The effect of the presenting part may be important in increasing or decreasing the pressure. In considering the clinical as-

pects of this problem, it would seem that the perineal support and the effect of the presenting part must be considered in any determination of the forces necessary to rupture fetal membranes.

DR. STEPHEN F. NAGYFY, Binghamton, N. Y.—I, too, at one time, keenly felt the need to investigate the tensile strength of amniotic membranes. In so many instances of premature rupture of membranes leading to premature birth, it would be desirable to know whether inherent factors in the strength of the membranes may be responsible for early rupture of the bag of waters.

I was carried back to my resident years in 1939 when I conducted similar experiments. In order to reproduce the hydrostatic effect of fluid, I used water pressure behind the membrane. This, of course, presented a rather awkward problem, because a veritable shower occurred when the membranes were burst under pressures of 180-200 mm. of mercury. An inverted bell jar over the apparatus permitted visibility and kept the observer dry.

The apparatus which I devised for this study consisted of a double cylinder, the lower half of which was filled with water. Air was forced into this lower chamber by means of a sphygmomanometer bulb connected by a T tube to a mercury manometer to register the pressure within the chamber. The air pressure would cause a column of water to rise into the upper chamber. Rubber gaskets with apertures of 2 or 4 cm. containing the strips of membrane were held securely over this upper water-filled chamber by means of a screw washer. A diameter of 2 cm. was selected in order to simplify the computation of formulas with 1 cm. radius.

The bubble of membrane at times would exceed a hemispherical contour. The most disconcerting phase of the experiment would occur when leakage took place around the edges of the membrane, or the membrane slipped from within the gaskets. After testing some fifty or sixty samples, I gave up when it did not appear that I could formulate any degree of correlation between the tensile strength of the membrane, the degree of cervical dilatation, and the progress of labor.

If one takes a portion of the membranes near the placental margin the tensile strength may be greater than at a point taken several centimeters away. In order to arrive at an estimation of the tensile strength of membranes in the vicinity of the internal os, placentas with membranes obtained at cesarean section were selected. The area which would lie over the region of the internal os was trimmed to fit the apparatus, yet the values which I obtained were not consistent. In addition to setting the experiments at a reasonable time of day, I noted that the membranes would deteriorate after standing for a few hours, so that the values of bursting tension would be lowered. Keeping the membranes in saline solution in the refrigerator retarded the autolytic processes. I feel that it is important to conduct the tests on fresh membranes, that is, within twenty minutes to an hour after the placenta is obtained.

After performing numerous experiments and improving the apparatus I reviewed the literature to see whether any such investigations had been made. To my astonishment I discovered that an English obstetrician, J. Matthews Duncan,* conducted similar studies nearly a hundred years ago. His apparatus, as I recall, was very much like the one Dr. Danforth constructed.

The amniotic membranes with the chorion and decidua are quite thin, perhaps 2 or 3 cells in thickness. The amniotic layer is the strongest. As the membrane is distended under pressure, especially with the drying effect of air, it is very likely that the bursting tension may be lowered. I would like to urge Dr. Danforth to continue his experiments using water to burst the membranes. I feel that renewed interest in this study and further clarification of factors affecting the tensile strength of membranes may lead to a better understanding of causes of premature rupture of membranes.

*Duncan, J. M.: Tr. Roy. Soc. Edinburgh, vol. xxiv (1867). Reprinted in Researches in Obstetrics, Edinburgh, 1868, A. & C. Black, p. 299.

DR. DANFORTH (Closing).—Although our study does not make any positive contribution to the problem of spontaneous rupture of the membranes, I think it does virtually rule out one very important possibility, namely, inherent differences in strength of the membranes as the primary causative factor. I wish to thank Dr. Nagyfy for directing our attention to this work which has preceded ours, and of which, very frankly, we were entirely unaware. Dr. Nagyfy mentions the desirability of employing fluid, specifically water, in preference to oxygen as a source of pressure. If any solution other than amniotic fluid were used this too would introduce an error. Since we were interested in detecting differences between membranes, and since a uniform error was introduced in all of them, I believe that the results obtained with our relatively simple apparatus compare favorably with those which could be obtained with a more complex apparatus which merely introduced a uniform error of another kind.

Dr. Nagyfy mentioned also the importance of testing the membranes immediately. It so happens, as is mentioned in the paper, that in this study the membranes were tested promptly after delivery. However, out of curiosity, we did test several membranes, running samples at intervals up to 24 hours. There was no significant difference between any of the specimens, suggesting that instant testing after delivery was not essential.

CIRCUMVALLATE PLACENTA*

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PLACENTAL pathology has been the subject of an increasing number of studies reported in recent obstetric literature. This trend is good, as this intermediary organ between the mother and the fetus is responsible for many complications of pregnancy and labor. One type of pathology of this organ that has been neglected, and often misunderstood, is circumvallate placenta.

Standard textbooks on obstetrics have given scant attention to this condition, and minimized its significance. Williams[1] stated, "Upon going over the clinical histories of patients presenting the abnormality, my impression is that it is practically without clinical significance, and is to be regarded merely as an interesting anatomic condition." DeLee and Greenhill[2] give few factual data about the clinical significance of circumvallate placenta, while devoting an entire chapter to placenta previa. There is also a paucity of reports regarding this entity in the current literature.

In the course of this study of circumvallate placenta, a significant amount of pathology was found. We were impressed with the high incidence of maternal hemorrhage, late abortions and premature labors. The fetal loss is high, yet current fetal mortality reports rarely list circumvallate placenta as an etiological factor. In presenting this study, it is our desire to call to your attention the clinical significance of this entity.

Our data are obtained from 8,562 consecutive deliveries at Butterworth Hospital, Grand Rapids, Mich., between June 1, 1949, and May 31, 1952. Circumvallate placenta occurred 41 times, giving a ratio of one in 208 deliveries. Hobbs and Price[3] reported the incidence as one in 138 cases. Hunt, Mussey, and Faber[4] reported one in 188 cases. Our incidence may be slightly lower because all abortions prior to 20 weeks of gestation were excluded.

Clinical Findings

In this series of cases of circumvallate placenta, there were 12 patients who had no symptoms prior to delivery. However, 3 of these 12 had complications of delivery, so that there were only 9 cases in which this entity was clearly an incidental finding. Thirty-five patients were multiparas; 6 were primiparas.

The most common symptom presented was vaginal bleeding (Table I). Twenty-one (51.2 per cent) patients bled, and of these, 11 (26.8 per cent) hemorrhaged severely enough to require transfusions. In 7 (17 per cent) instances the bleeding was so alarming that immediate sterile vaginal examina-

*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

tions were done in the operating room, set up for cesarean section. The bleeding was usually intermittent in character. It started prior to viability of the fetus in 17 of the 21 patients who bled. This differs from placenta previa and abruptio placentae, where the initial hemorrhage usually occurs after 28 weeks of gestation. In 8 patients in this series bleeding began as early as the first trimester.

TABLE I. CLINICAL FINDINGS

SYMPTOM	NUMBER	PER CENT
No symptoms	12	29.3
Bleeding	21	51.2
Transfusions	11	26.8
Hydrorrhea	11	26.8
Intermittent contractions	8	19.5
Third-stage complications	6	14.6

The second most common symptom in this series was hydrorrhea gravidarum. A watery vaginal discharge occurred in 11 cases (26.8 per cent). In 9 of these it was also associated with bleeding. It is often difficult to differentiate this drainage from that of ordinary rupture of the membranes. In a report on the use of progesterone to delay onset of labor after premature rupture of the membranes, Eichner and Kunin[5] were unable to differentiate hydrorrhea gravidarum from ordinary rupture. They did not mention placental abnormalities as a cause of hydrorrhea. Other authors[1, 3, 4] have stated the importance of this symptom in the diagnosis of circumvallate placenta. This placental abnormality should be considered whenever hydrorrhea gravidarum occurs.

Another common finding in this series was the occurrence of intermittent uterine contractions. Eight patients presented this symptom, often at the time of vaginal bleeding or hydrorrhea. This may be explained as an irritation of the myometrium by fluid or blood, as it dissects the amniotic sac from its attachment to the decidua vera. It was often difficult to determine whether or not a patient with these contractions was in premature labor. Several patients had repeat hospitalizations.

Table II summarizes the stage of pregnancy at which symptoms began. About half of the patients had bleeding, hydrorrhea, or contractions prior to the viability of the fetus. Excluding those without symptoms, the average onset of symptoms was at 20.5 weeks of gestation. So when this symptom complex presents itself in pregnancy, particularly before 28 weeks of pregnancy, circumvallate placenta should be suspected.

TABLE II. ONSET OF SYMPTOMS

	WEEKS	NUMBER	
Before Viability of the Fetus.—			
	0-8	6	
	9-12	3	
	13-16	1	
	17-20	4	
	21-24	5	
	25-28	1	
			20
After Viability of the Fetus.—			
	29-32	3	
	33-36	5	
	37-42	1	
			9
	No symptoms		12
	Total		41

Premature labor was experienced by the majority of the patients in this series, as shown in Table III. Only 15 patients (37 per cent) delivered after 37 weeks of gestation. The average length of pregnancy was 34 weeks. Consequently, prematurity of the infant presented a major problem. There were 8 stillbirths, and 4 early neonatal deaths. Table IV summarizes the fetal survival as to weight. The average weight of all infants in this series was 2,393 grams. All 11 infants under 1,500 grams died. Only one of 7 infants between 1,500 and 2,500 grams was lost, while all infants over 2,500 grams survived. The gross fetal loss was 29.2 per cent.

TABLE III. TIME OF DELIVERY

WEEKS	NUMBER		
Premature.—			
Prior to 21	1		
22-25	6		
26-29	2		
30-33	7		
34-37	10		
		26	(63%)
Term.—			
38-42	15		
		15	(37%)
Total		41	

TABLE IV. INFANT SURVIVAL

WEIGHT	NUMBER	SURVIVED	
		NUMBER	PER CENT
Under 1,500 grams	11	0	0
1,500-2,500 grams	7	6	85.7
Over 2,500 grams	23	23	100
Total	41	29	70.8

Complications of the third stage of labor are seen fairly frequently with circumvallate placenta. These consist mainly of (1) improper separation of the placenta, and (2) shearing of the membranes from the placenta. In this series the third stage of labor was complicated 6 times (14.6 per cent). Manual removal of retained secundines was required 3 times, and each of these patients was transfused for hemorrhage. In one case pieces of retained placenta were thought to be the cause of endometritis and parametritis. In another instance the placenta separated late in the second stage of labor and delivered with the baby's feet. This infant had asphyxia pallida, but responded to treatment. It is important to examine closely a circumvallate placenta and its membranes to avoid returning a patient to bed with an incompletely evacuated uterus, and the concomitant danger of postpartum hemorrhage.

Management

The management of the cases reported in this series varied according to their symptoms. There is no specific therapy for a condition in which only a presumptive diagnosis can be made. In general, the management was directed toward preserving the pregnancy to term, when possible, without jeopardizing the mother's life. Expectancy was the keynote, unless bleeding or other complications were severe enough to demand definitive therapy. Patients with intermittent contractions or hydrorrhea were placed on bed rest and observed. In a few selected cases with copious watery discharge, prophylactic antibiotics were given.

When bleeding was a predominate symptom, blood was typed and crossmatched and held in readiness. Seven patients hemorrhaged severely enough

prior to delivery to require definitive therapy. These patients were subjected to sterile vaginal examinations to determine the cause of bleeding. Three of these were suspected to have had placenta previa, and another abruptio placentae. The sterile vaginal examinations aided in establishing a correct diagnosis. In 3 cases amniotomy to induce labor was performed at this time. Induction of labor may be necessary at times in circumvallate placenta to reduce morbidity from hemorrhage.

Case Histories

Two cases were selected to illustrate some of the various symptoms and complications of circumvallate placenta. The first case demonstrates the classical symptoms of circumvallate placenta, fetal loss due to a premature labor, and third-stage complications.

CASE 1.—A 25-year-old white woman was admitted to the hospital Oct. 1, 1949, at 23 weeks of pregnancy. For 7 days she had had episodes of intermittent mild bleeding, and leakage of watery fluid from the vagina. On the day of admission irregular uterine contractions had begun.

Past history revealed that this was her seventh pregnancy. She had had one normal term delivery and 5 early abortions. Her last menstrual period was May 2, 1949.

Admission examination revealed a uterus the size of a 5 months' gestation. Fetal heart tones were present. The patient's condition was good. She was placed upon bed rest and given sedation. Penicillin in doses of 300,000 units was administered twice daily. The bleeding, hydrorrhea, and uterine contractions gradually subsided, and she was discharged after 5 days' hospitalization.

Pregnancy then progressed fairly normally at home for 6 weeks, although there were recurrent minor episodes of hydrorrhea and bleeding. On Nov. 19, 1949, at 29 weeks of gestation, she awoke at 4 A.M. with severe uterine contractions and soon passed a premature infant with several large blood clots. A circumvallate placenta was delivered spontaneously, but she continued to bleed severely. She was brought into the hospital in shock. The usual treatment for shock was carried out, including transfusion of whole blood. She was then placed upon the delivery table, where several pieces of placenta were removed with an ovum forceps and a curette. The uterus was packed with gauze and the patient returned to bed. She received 2,500 c.c. of whole blood intravenously. Her recovery was uneventful thereafter, and she was discharged on the sixth postpartum day. The infant weighed 995 grams and died at 48 hours.

This second case demonstrated the confusion between placenta previa and circumvallate placenta, and the value of a sterile vaginal examination.

CASE 2.—A 32-year old white woman was admitted to the hospital on May 27, 1949, at 37 weeks of gestation. She had had 3 previous normal term pregnancies and one early abortion. The present pregnancy had been uneventul until the day of admission, when she awoke in the morning in a pool of blood. She had no pain or contractions. The husband estimated "more than a cupful of blood" had been lost. Continuous bleeding was present on entry into the hospital, although she was not in shock. A transfusion of whole blood was started, and the patient taken to the operating room, set up for cesarean section. Sterile vaginal examination revealed a soft, boggy cervix, which was dilated 3 cm. No placenta could be palpated. The membranes were ruptured with an Allis forceps. Labor soon began, and 4 hours later she delivered a healthy male infant weighing 3,157 grams. After a third stage of 2 minutes, a typical circumvallate placenta delivered. The postpartum course was uneventful.

Comment

Circumvallate placenta is an important complication of pregnancy which the obstetrician must manage fairly frequently. In the first place, this series and those of other authors[3, 4] have shown that it occurs almost as often as does

placenta previa. Second, it is associated with a high percentage of maternal and fetal complications. Furthermore, the diagnosis of this condition is difficult. It is extremely important to be aware of circumvallate placenta, for although there is little definitive therapy, it is a serious error to treat patients actively for the mistaken diagnosis of placenta previa. We wonder how many are sectioned for circumvallate placenta by those who routinely subject to section, without vaginal examination, all patients with bleeding in the last trimester of pregnancy.

Hemorrhage, infection, and third-stage complications are the vital threats to the mother. Hunt, Mussey, and Faber[4] stated that hemorrhage is seldom profuse in circumvallate placenta. In this series there were 7 patients immediately examined because of hemorrhage. Four others hemorrhaged during the third stage of labor. In all, 11 patients were given transfusions. Bleeding was less severe in another 10 cases, but in these it still presented a source of anxiety to the patient, her family, and the obstetrician.

The bleeding in these patients may come from minimal separations of the placenta, but more probably comes from a rupture of a marginal sinus. Fish and his associates[6] have stated that rupture of the marginal sinus was responsible for a third of all bleeding in the last trimester of pregnancy. Donnelly[7] found that 50 per cent of patients with abnormal placentas had bleeding during pregnancy or labor. Harris[8] reported that in circumvallate placenta both the superior and inferior walls of the sinus may be composed of decidua. He also showed the marginal sinus to communicate with the maternal venous system. Thus, whatever the mechanism of bleeding in circumvallate placenta, it is mainly maternal, and an important complication of pregnancy.

The second threat to the mother, namely, infection, was infrequent in this series. Only 2 patients developed morbidity. One patient had fever for 5 days following a cesarean section for pre-eclampsia. The circumvallate placenta was an incidental finding in this case. The other patient had endometritis and parametritis, thought to be due to retained pieces of placenta. However, the potential for ascending infection is ever present in patients with an open cervix and intermittent bleeding or hydrorrhea. Hunt and his associates[4] have commented on this mode of infection. Perhaps the use of antibiotics in selected cases is valuable in reducing this danger.

The third threat to the mother is a complication of the third stage of labor. Retained placenta or membranes may produce hemorrhage. Six of 41 patients in this series presented third-stage complications. Hobbs and Price[3] reported 12 instances of retained secundines in 150 cases. Routine careful inspection of all placentas, and manual removal of any retained pieces, should reduce the morbidity from hemorrhage and infection.

The prime threats to the fetus are abortion and premature labor. Seventeen per cent of the patients aborted before viability of the fetus, and 46 per cent had premature labors. Thus, a total of 63 per cent of the patients failed to carry their pregnancies to term. The gross fetal loss was 29.2 per cent. This figure compares with the fetal mortality of 33 per cent reported by Hobbs and Price,[3] and 26 per cent reported by Hunt, Mussey, and Faber.[4]

Placental deficiency is the probable cause of fetal death in utero. This is due either to infarction, or to restriction of growth of the placental plate, so that the placenta is unable to meet the progressively greater demands of the fetus as pregnancy continues. No other factors entered into the fetal mortality in this series.

The diagnosis of circumvallate placenta cannot be made with certainty until labor is completed and the placenta inspected. However, there are often enough of the symptoms previously described so that a suspicion of this condition can be entertained. This was true in 12 of the 41 cases in this series,

evidenced by a written diagnosis of "circumvallate placenta" on the patient's chart prior to delivery. Other authors[3, 4] have discussed in detail the symptoms which lead to a correct diagnosis.

The predelivery diagnosis is most often confused with placenta previa. However, there are some characteristics which help differentiate these two conditions. Hydrorrhea is rarely present in placenta previa. Bleeding in circumvallate placenta usually occurs earlier than in placenta previa. It is also less profuse, and often accompanied by uterine contractions. It is not likely to be more severe with successive episodes of bleeding. Finally, placentograms and sterile vaginal examinations, which may clinch the diagnosis of placenta previa, are negative in circumvallate placenta.

Abruptio placentae is another condition commonly confused with circumvallate placenta. Classically, abruptio placentae presents as an acute single episode with severe pain, tonic uterine contractions, shock, and signs of fetal distress. In circumvallate placenta the symptoms are intermittent, pain is minimal, the uterine contractions are mild, and shock is unusual. However, some patients with circumvallate placenta subsequently develop an abruption. Sexton and his associates[9] have shown that premature separation may be initiated by the degeneration of trophoblastic decidual areas at the margin of circumvallate placentas. They reported 82 instances of circumvallate placenta in 476 cases of premature separation. Thus, the two conditions may be associated. In one case in this series, abruptio placentae occurred late in the second stage of labor. The infant had asphyxia pallida at birth, but survived.

One final point might be made regarding the importance of circumvallate placenta. We have surveyed several articles in the current literature on the causes of death of premature infants.[10-14] Placental abnormalities are mentioned as a group, but circumvallate placenta is unnoticed as a specific factor. Yet this study has shown that circumvallate placenta plays almost as important a role in fetal loss as does placenta previa and abruptio placentae. Obstetricians should be alert to note and record circumvallate placenta, so that its importance in the etiology of premature labors and infant mortality may be more accurately ascertained.

Conclusions

1. Experience with 41 cases of circumvallate placenta in 8,562 consecutive deliveries has been presented to demonstrate the clinical significance of this condition in obstetrics.

2. Intermittent vaginal bleeding, hydrorrhea, and uterine contractions are the common symptoms which lead one to suspect the presence of circumvallate placenta.

3. The predelivery diagnosis is most often confused with placenta previa and abruptio placentae.

4. Management of patients with circumvallate placenta is principally expectant, although bleeding in some cases demands definitive treatment.

5. The vital threats to the mother are hemorrhage, infection, and third-stage complications.

6. The fetal survival rate is low, due primarily to late abortions and premature labors.

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Discussion

DR. ARTHUR B. HUNT, Rochester, Minn.—J. Whitridge Williams has probably presented the best evidence for the etiology of placenta circumvallata. His typically careful studies in 1927 advanced the theory propounded by Robert Meyer in 1909 and originally set forth by Schatz and von Herff. This theory held that the chorion frondosum was excessively smaller than the chorion laeve and that if the pregnancy is to continue the periphery of the placenta must invade the decidua at the edge of the placenta by oblique extension of the villi. This results in a virtual splitting of the decidua into two lamellae, the uterine portion being the decidua basalis and the other persisting as a covering layer over the extrachorionic portion of the circumvallate placenta. Unfortunately, Williams' careful placental studies were accompanied by a rather dogmatic opinion that circumvallate placenta had no clinical significance. This view was expressed in spite of earlier German pronouncements to the contrary but it may account for the rather long period during which American obstetricians thought that circumvallate placenta was of no clinical importance. We are indebted primarily to Hobbs of St. Louis, who, with Rollins in 1934 and again with Price in 1940, conclusively showed many of the clinical features of placenta circumvallata which Drs. Paalman and Vander Veer have so well discussed today.

Two conditions producing uterine bleeding in pregnancy can be associated with circumvallate placenta, namely, rupture of the marginal sinus, as described by Fish, Bartholomew, Colvin, and Grimes, and abruptio placentae, as recognized by the Boston group. These two conditions more frequently occur unassociated with circumvallate placenta. In our experience circumvallate placenta seldom produces severe abruptio placentae. I am at a loss to explain why Dr. Paalman has encountered more severe hemorrhage in circumvallate placenta than Drs. Mussey, Faber and I did. Our experience in 47 instances and many subsequent cases is closer to that of Hobbs, who seldom found the bleeding to be very severe, but as more cases are accumulated this opinion may need revision. Like the essayists, our group has often been able to make a correct presumptive diagnosis of circumvallate placenta ante partum. We found one rather important fact about circumvallate placenta in that the recurrence rate in other pregnancies approached 20 per cent and in some cases caused repeated birth of premature infants.

In the drive to reduce fetal mortality any condition which gives a fetal mortality of one-fourth to one-third of the cases merits accurate diagnosis. It is true that therapy leaves much wanting, but in some cases around the border line of viability complete bed rest for a few days may make a substantial difference in fetal outlook. The incidence of circumvallate placenta is nearly as great as that of placenta previa and the fetal mortality is higher than in many series of cases of placenta previa reported in recent years. Because of this, one can urge that obstetricians spend a few seconds in careful observation of the fetal surface of the placenta, because in those cases that give rise to premature delivery the circumvallate placenta is usually a complete and very evident anomaly.

In conclusion I should like to commend Dr. Paalman and Dr. Vander Veer for their presentation and express the hope that it will not go unregarded but will contribute to the more accurate diagnosis of this condition in obstetric practice.

POSTPARTUM CONVULSIONS*

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THERE has been a recognized gradual shift in the major causes of maternal mortality from the previously accepted triad of infection, hemorrhage, and toxemia.[1-3] Infection and hemorrhage have been almost entirely eliminated in some institutions as causes of maternal mortality. Conditions coincidental to pregnancy now cause the greater percentage of the deaths. However, all institutions are plagued by the constantly present menace of toxemia. Nationally, toxemia accounted for 3.3 deaths per 10,000 live births in 1948.[2] In Milwaukee Hospital toxemia accounted for 18.6 per cent of the maternal deaths from 1934 to 1949. There have been no maternal deaths due to toxemia in this series of 14,513 cases. If a constant vigilance is to be continued so that the excellent maternal mortality records established in all major institutions will not result in a damaging complacency, we must continue to attack every phase of the toxemia question.

Our attention was directed to this problem by the fact that though there were no cases of antepartum eclampsia during the year of 1951, there were five instances of postpartum convulsions. This seemed unusual; therefore the records for five years of deliveries were reviewed.

Incidence

During the period of 1947 to 1951, inclusive, 14,513 patients were delivered at Milwaukee Hospital. During this period toxemia was recorded in 331 instances, an incidence of 2.28 per cent. Pre-eclampsia was recorded in 317 patients. There were 14 instances of eclampsia. Antepartum and intrapartum convulsions occurred 5 times while postpartum convulsions occurred 9 times. When figures such as these are uncovered, an analysis of the entire problem is essential. Dieckmann[2] presents the over-all incidence of toxemia in hospital deliveries as being 8 per cent. Our incidence for 14,513 deliveries as shown in Table I is 2.28 per cent. So that our interpretations may be clarified, a definition of our understanding of toxemia is necessary. Any two of the three cardinal findings, hypertension, proteinuria, and edema, catalogued the patient as toxic. A patient was considered hypertensive if the blood pressure reached 140/90. These have been our standards.

As seen in Table II, 9 of the 14 cases of eclampsia were postpartum in type. This is contrary to the usual experience. In our experience by percentage, antepartum convulsions occurred in 35.7 per cent of the cases, while postpartum convulsions occurred in 64 per cent. Dieckmann[2] states the incidence

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of postpartum convulsions at Chicago Lying-in to be 25 to 45 per cent. Eastman[4] refers to the incidence as 25 per cent. Greenhill sets the incidence at 20 per cent.

TABLE I. INCIDENCE OF TOXEMIA

YEAR	DELIVERIES	PRE-ECLAMPSIA	ANTEPARTUM OR INTRAPARTUM ECLAMPSIA	POSTPARTUM ECLAMPSIA
1947	2737	47	0	1
1948	2772	45	1	1
1949	2954	60	3	0
1950	3033	63	1	2
1951	3017	102	0	5
Total	14,513	317	5	9

We are aware of the fact that our incidence of toxemia is supiciously low. We attribute this to several factors: (1) Practically all patients were white. (2) All were private patients attended by carefully selected general practitioners of a very high caliber, or in the majority of instances by Board or Board-eligible obstetricians. (3) For practical purposes, no patient entered without prenatal care. (4) An established resident training program assured the patient and staff man of accurate and efficient observation in case of impending or frank complications. Both our rates of pre-eclampsia and antepartum eclampsia could be attributed to the above-mentioned factors.

What was the cause of the unusual proportion of postpartum eclampsia and what is its significance? It is felt that this is a very important and dangerous complication of pregnancy. The generally accepted maternal mortality rate for postpartum eclampsia is quoted as 16 per cent.[2] The importance of this condition is magnified when we find that in most of our cases there was no reason to suspect serious postpartum complications. Neither in our series nor in the cases quoted from Chicago Lying-in were there any deaths. However, the fact that it is almost impossible to predict when postpartum eclampsia might occur makes this problem worthy of increased attention. The necessity for increased emphasis was impressed upon us when a search of the literature of the past ten years revealed only two publications concerning this condition. Let us not lower our guard.

A word of warning—not all convulsions are the result of toxemia or associated with the problem of pregnancy. Any patient in the labor and delivery rooms may have entered with convulsions due to uremia and agranulocytosis, as was the situation in one of the cases of our series catalogued as antepartum eclamptic toxemia. There is nothing to prevent the pregnant patient from having a central nervous system lesion with convulsions, as was the case in another patient. Although these cases are in this series, and are reported as antepartum eclamptic toxemia, it is our feeling that the conditions causing these convulsions were coincidental to pregnancy. It therefore becomes the duty of the attending obstetrician to determine the existence of any pathological conditions that might confuse the picture of pregnancy during the prenatal period and send adequate warning to the hospital. This information should be supplied when the patient is originally registered and again with the patient when she enters for delivery. Accurate prenatal care is the answer to this. The epileptic will then not be treated as an eclamptic patient.

Analysis of Cases

The reported cases of postpartum convulsions were all carefully evaluated and were without conditions that might have complicated the accuracy of the diagnosis.

TABLE II. FINDINGS ON ADMISSION

PATIENT	AGE	PARA	GRAVIDA	NO. WEEKS' GESTATION	WEIGHT (POUNDS) GAIN	EDEMA	ALBUMIN	BLOOD PRESSURE
E. C.	*38*	0	i	40	35		0	170/108
R. C.	25	0	i	40	11		20 mg.	142/90
M. D.	19	0	i	40	?		3,000 mg.	156/104
A. M.	25	0	i	41	14	0	0	130/80
M. K.	24	0	i	38	18		0	136/86
E. H.	20	0	i	40	25		0	134/98
M. S.	18	0	i	42	*41*		50 mg.	125/80
D. D.	18	0	i	42	*43*	0	0	132/84
L. E.	33	i	ii	40	27		5,000 mg.	142/80

An analysis of Table II reveals that all patients but one were primigravidas. Two of the patients were above the age of 25 years. The average weight gain fell within the normal limits, except in 3 instances. Edema was present in all but 2 cases. Proteinuria was found in 4 cases. In 4 cases the blood pressure readings conformed to the accepted standard of hypertension. None of the patients had a history of any previous type of convulsive seizure. There was no evidence of gross anoxia during or immediately following the general anesthesia. All patients were given sedation during labor with a barbiturate and Demerol, Demerol and scopolamine, or all three. In 5 of the cases there was evidence of prepartum toxemia, but none of these could be considered fulminating. It is felt that an element of surprise resulted from 4 of the cases in which there was one of the cardinal findings, but which were not classified as frank toxemia by the accepted standards.

Analysis of Table III, recording time relationship, reveals the average length of labor to be 7.43 hours. All convulsive seizures occurred within the first 24 hours, in fact within 13 hours post partum. The number of convulsive seizures varied from 1 to 9. Although the blood pressure tended to rise with a convulsion, there was very little variation.

TABLE III. TIME AND BLOOD PRESSURE RELATIONSHIPS

PATIENT	LENGTH OF LABOR (HOURS)	INTERVAL BEFORE CONVULSIONS (HOURS)	NO. CONVULSIONS	BLOOD PRESSURE DURING CONVULSION	BLOOD PRESSURE AFTER CONVULSION
E. C.	4½	8	6	180/105	185/110
R. C.	4½	3	1	180/90	140/92
M. D.	12	6	1	165/90	140/70
A. M.	7½	6	2	165/95	170/110
M. K.	4	7	2	138/95	145/85
E. H.	20	11	1	140/100	132/80
M. S.	6½	13	9	135/90	135/92
D. D.	6½	11	1	150/100	132/84
L. E.	1¼	8	1	110/70	150/88

Immediate treatment instituted by the resident staff resulted in complete recovery in all cases. All patients were free of edema and had recorded pressures that varied between 102/80 and 140/92 on discharge. Examination of the eye grounds revealed no abnormalities. The attending obstetricians have reported their patients as completely recovered from the described incidents.

A résumé of the treatment is shown in Table IV.

Milwaukee Hospital is a private institution; therefore, there are no set routine procedures of treatment, except the essential starting routines for emergencies. After the initial therapy has been instituted, and after the at-

tending obstetrician has been contacted, the method of treatment is directed by him. This explains the fact that only morphine sulfate, barbiturates, and diet were the common factors used in all cases.

TABLE IV. RÉSUMÉ OF TREATMENT

PATIENT	MORPHINE SULFATE	MAGNESIUM SULFATE	HYPERTONIC GLUCOSE	BARBITURATES	SALT-FREE DIET	OXYGEN	TRANSFUSIONS
E. C.	+	0	+	+	+	+	+
R. C.	+	0	+	+	+	+	0
M. D.	+	+	+	+	+	0	0
A. M.	+	+	+	+	+	0	0
M. K.	+	0	0	+	+	0	0
E. H.	+	0	+	+	+	+	0
D. D.	+	+	0	+	+	+	0
M. S.	+	0	0	+	+	+	0
L. E.	+	0	+	+	+	+	0

Comment

What determines that a case will become eclamptic? What precipitates convulsions in these cases? One can speculate that these were all either cases of moderately pre-eclamptic toxemia or preclinical threshold cases that were thrown into a convulsive state by one of several factors: the general anesthesia, which was used in all, the trauma and exertion of labor, or by the fact that these patients were actually more toxic than was recognized on the basis of the present standards of toxemia. All three seem reasonable and the last seems to be gaining support. Mukherjee and Telford[6] believe that consideration of impending danger is necessary when the blood pressure reaches 130/90. Whitacre[7] asks whether a systolic of 135 would not be a better level at which to set the danger point. It is not our intention to report nine cases of postpartum convulsions or to emphasize our method of therapy. We are, however, interested in calling attention to the fact that, at a time most unsuspected by the attendants, convulsions can occur. This, as previously stated, carries with it a mortality rate of 16 per cent. On our service emphasis has always been placed upon the fact that all postpartum patients, especially those who have had general anesthesia, must be observed with the same routine care given the patient who has had a major operation. This is especially true if we are to uncover the case which might prove a surprise to us. All postpartum observation must include systematic blood pressure readings. Since the above has been a generally accepted procedure and since January, 1952, when all patients even with mild pre-eclamptic symptoms have been heavily sedated, and treated with measures to control central nervous system irritability and the retention of excess tissue fluid, there have been no cases of postpartum eclampsia. It is worth mentioning also that there have been no cases of antepartum eclampsia during this time.

It is essential that it be emphasized and re-emphasized that the key to good obstetrics still lies in exacting and conscientious prenatal care. A good history will still be the lead to important revelations. One of us, in searching for similar cases in our hospital, discovered a case which fitted the category. A convul-

sion occurred on the second day post partum. Mild toxemia existed. The history, taken more completely and with the aid of an interpreter after recovery from the episode and after the case had been handled as eclampsia, revealed that this patient had been treated for similar episodes by her family doctor before pregnancy. This was evidently epilepsy, and the patient was transferred to that service. It is essential again to emphasize the importance of the history and the necessity of re-evaluating the present standards of toxemia. This is necessary so that we may be alerted to the dangers inherent in the case that shows mild to moderate signs of pre-eclamptic toxemia.

Summary

1. A review is made of 14,513 deliveries at Milwaukee Hospital.

2. There were 331 instances of toxemia, which included 14 cases of convulsive toxemia. Cases of hyperemesis gravidarum have not been included.

3. In 9 of the cases of eclampsia the convulsions occurred in the postpartum period. These were in patients who had only mild to moderate pre-eclamptic toxemia. The convulsions were not anticipated because of the absence of severe symptoms.

4. An effort is made to emphasize the importance of the inherent dangers of the postpartum period, especially in patients who have mininal manifestations of toxemia.

5. The importance of accurate histories and careful prenatal care is re-emphasized.

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Discussion

DR. PERRY J. WILLIAMSON, Memphis, Tenn.—The essayists have mentioned the need for more clarity in our understanding of the toxemias of pregnancy. With this we heartily agree. Webster's Dictionary indicates that a toxin is a poison formed as a specific secretion product in metabolism. The supposition has generally been that the placenta produces a toxin or poison, and with that we do not agree. It is probable that the placentas of toxemic and nontoxemic patients produce the same substance. It is also probable that the placenta is a stimulus to the production of a syndrome of symptoms and signs which we recognize and call toxemia of pregnancy. The better-cared-for patients can neutralize these products, while those less fortunate may not. In all surveys of this disease, the fact remains that the patients usually have not received care adequate to prevent this condition.

At the Milwaukee Hospital, in the five-year period discussed, 14,513 patients were delivered. Of these, nine had postpartum convulsions, but none died. They consider that any two of the findings of hypertension, proteinuria, and edema indicate that the patient was toxemic. Our understanding of the toxemias of pregnancy is comparable.

In the same period of time, from 1947 to 1951 inclusive, we were responsible for the delivery of 25,174 patients. Actually 18,334 were delivered in the hospital and the remainder in their homes, but as all of those with complications of labor and delivery must come into the hospital, many of whom were toxemic and some of them in convulsions, it is necessary to consider the total. This is also not accurate, because some of the patients came from Arkansas and Mississippi, and had never been seen by our service before being admitted as emergency cases.

At the moment the best we can do is to mention our responsibility for delivering 25,174 mothers, among whom 160 had convulsive seizures, which we thought to be eclampsia. Of these, 43 cases were considered to be postpartum eclampsia. Some have arbitrarily indicated that postpartum eclampsia occurs in those patients who have had their first convulsion 30 hours after delivery. We have been able definitely to establish only that these 43 women had no convulsions prior to delivery.

The majority of these patients were treated in approximately the same manner. As they had all been delivered, surgical treatment did not come into the question. They were given barbiturate drugs for sedation, and fluids, depending upon the patient's need. In most cases no hypertonic glucose was used, but rather hydration therapy of approximately 4,000 c.c. of isotonic glucose solution in 24 hours. Intravenous isotonic fluid must be given very slowly, no more than 60 drops to the minute, with the head of the bed elevated, and should be discontinued when the patient regains consciousness and can take fluid by mouth.

One patient died. She was a 38-year-old gravida i, para i, who was delivered by a private physician at her home, and admitted to the hospital five hours later in coma, after having had two convulsive seizures. Although normal physiology was restored, she did not regain consciousness, nor did the hypertension recede below an average of 200/100. She died 44 days after admission to the hospital. The spinal fluid indicated that an intracranial hemorrhage had occurred. Our case histories concur with the opinion of the essayists, that serious developments may ensue without marked antepartum indications.

It is probable that the quality of the attending staffs at the John Gaston Hospital and the Milwaukee Hospital is comparable, and that our resident training program is the equal of theirs. It is also probable that the results obtained in terms of the salvage of human life in any one of the private hospitals in Memphis would be comparable with those of the Milwaukee Hospital. The results of our city hospital, however, cannot at this time be compared with those of private hospitals, but we are doing the best we can to improve these results. Every pregnant woman is potentially a toxemic one, and marked improvement in the prevention of toxemia of pregnancy can be attained only by the better understanding and acceptance of well-planned prenatal care.

DR. HUGH G. HAMILTON, Kansas City, Mo.—I wish to cite one case to illustrate what can be a very probable answer to several of these postpartum convulsion cases, and that concerns the matter of the use of intravenous Ergotrate.

I would be interested in knowing if these patients of Dr. Hofmeister's received intravenous Ergotrate, and the mode of administration.

A few years ago, we performed an elective cesarean section under spinal anesthesia on a woman who had a perfectly normal blood pressure and no abnormality in her blood chemistry. She had no urinary pathology. As we did the cesarean section, as we opened the uterus, the woman was given her intravenous Ergotrate. Her blood pressure had been taken by the anesthetist just prior to this point, and found to be 112/72, as it had been throughout the course of the operation. Within 45 seconds of the administration of the Ergotrate, that patient—who had formerly been comfortable and relaxed—was moaning with pain in her head, and was threshing about on the table, complaining bitterly of the distress that she was undergoing with throbbing headache and blurring vision.

The patient was immediately given ¼ grain of morphine intravenously. Her blood pressure was taken prior to the administration of morphine and was found to be around 210 over 118.

We were unaware of this potential effect of Ergotrate, so, after she went back to her bed, we continued our routine administration of oral Ergotrate, intending to use it for the next 72 hours. With our continued administration of Ergotrate we produced a beautiful convulsion eleven hours post delivery. At this point we did stop our Ergotrate, and the patient straightened out and did well.

The following week we had another patient who did precisely the same thing on the table, but this time we were a little more alert to the problem, so we did not give the subsequent Ergotrate, and used only barbiturates.

This, then, led us to go into the subject of the hypertensive effect of intravenous Ergotrate, and our figures were interesting. They are not as high as Dr. Schade of Los Angeles reported; he reported a hypertensive effect in as high as 30 per cent of patients.

Our standard for indicating a hypertensive effect was a rise in blood pressure—systolic and/or diastolic—of 20 points. The blood pressures of these patients were taken immediately prior to the administration of the Ergotrate, ten minutes afterward, and thirty minutes afterward. In those who reacted with hypertensive effect, this was evident in all cases within a ten-minute period after the administration of the drug.

We ran over 200 cases consecutively according to this method, and then we switched to methyl-lysergic acid. We then found a significant decrease in the number of hypertensive effects. There was no relationship in age or parity; apparently it is a direct action of the drug.

Dr. Willis Brown went further with the subject, and has continued some other studies on it since. His figures are a bit different from ours, but the difference is that in his series he has not been giving as much premedication as we have. We have given premedication of Demerol and scopolamine, and some barbiturates; his treatment has been done strictly and completely post partum.

We also found that there was a greater incidence of hypertensive effect, with the production of convulsion, if the woman was delivered under regional anesthetics, under spinal anesthetics, and less if she were delivered under general anesthesia.

For articles bearing upon this subject I refer Dr. Hofmeister to Dr. F. F. Schade's paper in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in 1951 and to our article in the *Southern Medical Journal* in August, 1952. The work of Drs. Willis Brown and Edward Jungck is summarized in their discussion of the latter paper.

It is my feeling that Dr. Hofmeister is reporting a series of ergonovine-produced convulsions.

DR. HOFMEISTER (Closing).—None of these convulsive seizures came on as rapidly—following the administration of the medication at delivery—as Dr. Hamilton would indicate was true in his cases. In the majority of instances our patients were given Ergotrate, but all of the convulsions—all evidence of this pathological condition—occurred after the patient was returned to her room.

I would again emphasize the fact that the answer to controlling the question of toxemia is in prenatal care, and in considering the postpartum patient in the same light as we consider the postoperative patient, so that careful observation is given the patient when she is returned to her room, especially if she is delivered under a general anesthetic.

DYSMENORRHEA*

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IT REQUIRES some temerity to embark upon the discussion of a subject which has long frustrated the medical profession. We do so, however, because of our long-standing interest in the problem and our belief that repeated consideration represents an important avenue toward the clarification of its many challenging aspects. Most medical discussions reflect a healthy admixture of fact and philosophy. Since factual data of unequivocal character regarding dysmenorrhea are notably scarce, this report must, of necessity, be principally a disclosure of our own philosophy regarding the subject. It is also based on a review of the literature. While many answers to the dysmenorrhea problem are lacking, it is desirable that we have some understanding regarding its probable cause in order to comprehend its many manifestations and treatment.

We define dysmenorrhea as a syndrome, characterized by such subjective symptoms as uterine cramps, pelvic discomfort, nausea, vomiting, malaise, premenstrual tension, and other variable disturbances, occurring in association with menstruation. Some of these manifestations could be looked upon as distinct entities and subjected to individual consideration but, for our purposes on this occasion, this would be impractical.

The primary or intrinsic (essential) form is seldom accompanied by recognizable pathology of the pelvic organs. The secondary or acquired variety, on the other hand, is commonly associated with disease of the generative tract. Endometriosis is a good example of the latter. While classification of dysmenorrhea into the primary and secondary varieties appears to be desirable, the presence of menstrual discomfort and discernible pelvic pathology does not necessarily prove a cause-and-effect relationship. Menstrual discomfort is a problem with many facets. It has social and economic aspects which may be important. Considered from the standpoint of its many ramifications the dysmenorrhea problem is by no means a simple one. Consequently, it seems desirable that we confine our discussion to some portion of the subject and, to that end, we propose to limit our comments chiefly to primary dysmenorrhea. We believe that, generally speaking, secondary dysmenorrhea is better understood and presents somewhat less of a problem than is presently true for the primary variety.

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As stated earlier, recognizable pelvic disease is seldom found in patients recorded as having primary dysmenorrhea. Indeed, the absence of recognizable pelvic pathology is generally the basis for making the diagnosis of primary dysmenorrhea. In some instances this may represent faulty reasoning. The fact that a patient's pelvis is reported to be "negative" means only that in our present state of understanding, we do not recognize the existence of pathology. Perhaps the patient's ailment is truly the result of a functional disturbance or, possibly, the commonly observed underdevelopment of the generative organs is responsible and should be recognized as a true abnormality. With increased knowledge in the fields of vascular spasm, cellular chemistry and electropotential, we may find an entirely acceptable answer to this problem. Meanwhile the term primary dysmenorrhea is merely a handle which enables us to segregate those dysmenorrheic patients without recognizable pelvic disease from those with evidence of pathology. Fundamentally, the cause of the discomfort may be the same in both instances. We believe the so-called primary variety greatly predominates and is the type present in many cases wherein some form of pelvic disease is also present.

While the clinical characteristics of primary dysmenorrhea are generally well known, their brief recapitulation here may not be out of place. Thus:

1. Primary dysmenorrhea generally begins within a year or two after the establishment of menstruation.

2. It commonly is crampy in character and frequently associated with constitutional symptoms such as nausea, vomiting, and/or premenstrual tension.

3. Histologic studies of the endometrium and temperature recordings reveal that primary dysmenorrhea seldom, if ever, occurs in the absence of ovulation.

4. Underdevelopment of the generative organs is not infrequently observed in these individuals. While this association suggests a cause-and-effect relationship, the association is not sufficiently consistent to warrant such conclusion.

5. Primary dysmenorrhea is most commonly diagnosed in the absence of palpable pelvic pathology.

6. With maturity and after the birth of a full-term fetus, primary dysmenorrhea tends gradually to disappear.

Incidence

About 70 years ago Jacobi[1] found that 50 per cent of young women complained of dysmenorrhea. For the majority the discomfort was mild in character and caused no real incapacitation. In a study of over 800 young college women and nurses reported by one[2] of us 25 years ago, a similar incidence was noted. Seventeen per cent complained of some incapacity while only 3 per cent were completely bedridden for the duration of the period. Since the vast majority of young women in this study group were found to be free from evidence of palpable pelvic disease, it is probable that the majority suffered from a primary type of dysmenorrhea. There exist few data at the present time to suggest that the incidence has materially changed. In this

connection it is of interest to note that during the past 10 years the number of absentees attributed to dysmenorrhea among women employees of one of the largest and best known Midwestern department stores[3] has actually decreased. In 1951, of a total 64,778 days lost because of illness, only 1,092, or approximately 1.5 per cent, were because of dysmenorrhea. While severe cramps and other subjective symptoms such as nausea doubtless curtail efficiency, the actual number of women work hours lost does not appear to be increasing. Even so, the annual accumulated time loss represents an exhorbitant sacrifice on the part of presumably healthy young women. What all this means in terms of dollar and cents loss to the afflicted individual as well as to the nation remains anyone's guess, but it requires no stretch of imagination to see that dysmenorrhea continues to be an important medical problem.

Cause of Primary Dysmenorrhea

If the mechanism involved in the production of menstrual pain were definitely known there would be little excuse for discussion of the subject. The cause of the pain in dysmenorrhea cannot be categorically stated. However, this does not mean we may not profit by examination of concepts regarding its origin and inspection of influential factors contributing to its occurrence and severity. While the cause of menstrual discomfort may someday be settled to everyone's satisfaction, the problem will not end until we have also learned how to prevent, or safely and completely control, the dysmenorrhea syndrome. Control of pain alone is not always sufficient since the associated constitutional symptoms such as nausea and/or vomiting are sometimes more important in determining the degree of individual incapacitation than is pain per se. Similarly, the accentuating effect of emotional tension upon menstrual discomfort must not be overlooked. In the clinical evaluation of dysmenorrhea, then, it becomes apparent that we must search for the underlying cause as well as the contributing factors which may play an important part in determining the degree of disablement.

Numerous theories regarding the cause of dysmenorrhea have been reported. As basic knowledge concerning the physiology of menstruation has increased, the older views have been replaced by more tenable explanations. The cervical stenosis explanation gave way to the concept of uterine underdevelopment. The once popular psychogenic explanation has been demoted to the position of an important influential factor. However, we must not be too hasty in minimizing the psychogenic factor. That emotional factors can play an important part has long been recognized. It is of interest to note in this connection that such keen observers as Drs. Carl Hartman[4] and G. van Wagenen[5] have noted little evidence to suggest that monkeys suffer from menstrual discomfort. Obviously one cannot draw conclusions from these observations since dysmenorrhea is largely a subjective syndrome. Since menstruation in the monkey is quite similar to that observed in the human being, one might expect that if dysmenorrhea occurred in the monkey it would cause recognizable indisposition.

Perhaps the most generally accepted view today is that menstrual discomfort is chiefly due to the hypercontractility of the uterine musculature.

However, many students of the problem are not entirely satisfied with this explanation. For them the prevailing myometrial theory is today being challenged by an increasing preference for an angiospastic concept as a cause for the discomfort. The myometrial concept that menstrual cramps are the result of strong uterine contractions has long been looked upon with favor. Presumably the mechanism is similar to the abnormal contractions of the bowel occurring in association with severe diarrhea and/or gas pains. Moir,[6] using intrauterine bags, was able to demonstrate that during the first half of the cycle (proliferative or estrogen phase) the uterine contractions were weak and of small amplitude. During the second half of the cycle (secretory or progesterone phase) he noted fewer contractions but of considerably greater amplitude. These observations, confirmed by others,[7, 8] suggested that uterine contractility was governed by such chemical regulators as the female sex hormones; that estrogen caused minimal uterine muscle activity while progesterone gave rise to considerable myometrial contractility. On the basis of these observations it seemed fair to assume that an imbalance of these chemical regulators, estrogen and progesterone, might well underlie the occurrence of menstrual cramps. Supporting this concept is the observation that menstrual pain seldom if ever occurs in the absence of progesterone, as during an anovulatory cycle. Furthermore, the administration of estrogen to women with primary dysmenorrhea may block the occurrence of uterine cramps. By the administration of 0.05 mg. Estinyl daily for 10 to 12 days, commencing immediately after the end of a period, Schuck[9] was able to prevent menstrual discomfort in 60 per cent of his dysmenorrhea patients. Schuck did not believe this therapy interfered with ovulation but unfortunately he was unable to prove this point by the performance of endometrial biopsies. It is possible, therefore, that in Schuck's series the estrogen interfered with ovulation, the bleeding episodes being anovulatory and painless in character.

Despite the frequent use of the term cramps in connection with the menstrual syndrome, close questioning of afflicted individuals will reveal that the cramps are merely a part of the picture. There is generally a background of discomfort variously described as a steady ache, bearing down, pressure, or just plain discomfort. Obviously, then, uterine cramps can explain only a portion of the dysmenorrhea syndrome. The undesirability, indeed, the impossibility of explaining the dysmenorrhea syndrome on the basis of a single abstract factor becomes apparent when we recognize and accept such interrelationships as hormonal regulation of uterine activity. Much more probable is the existence of a dysfunctional synergy (commonly temporary) between hormonal chemical regulators, myometrium, and other receptors such as the uterine vascular tree.

As previously stated, it does not seem feasible to attempt explanation of all symptoms making up the menstrual syndrome on the basis of a single factor. Something other than myometrial hyperactivity is necessary to explain the steady-ache type of discomfort, nausea and vomiting. To account

for these several explanations have been proposed, all of which point to disturbed circulatory function. Twenty-five years ago one of us attributed the steady ache to the superimposition of physiologic hyperemia of menstruation upon an already congested group of pelvic organs. The fact that in the majority of women the discomfort began before or at the time of the flow and disappeared within 12 to 24 hours encouraged this view. Also, many young women had already found that physical activity, such as an evening of dancing, did not increase the discomfort. This crude vascular concept led to a rugged era wherein physical activity played an important part in the therapy of dysmenorrhea. Many systems of exercises and relaxing programs were developed and advocated for young women with dysmenorrhea, especially college women. While these programs helped they were not a complete answer to the problem. Possibly the greatest value of the physical therapy era was the philosophical change it created regarding menstruation in general. The young women of a quarter century ago were taught not to restrict their activity; that, despite discomfort, menstruation was an essentially normal physiologic process. These young women of yesterday are the mothers of today and the healthy attitude instilled into them has been passed on to their daughters. Helpful as such philosophy regarding menstruation may be from a general point of view, it has brought little comfort to young women with severe incapacitating dysmenorrhea. For many sufferers there has continued to be a need for a better explanation and a more effective form of therapy. Today, a quarter century later, a vascular concept garbed in new clothing is still viewed with favor as a means for explaining the steady-ache portion of the dysmenorrhea syndrome. Now, with a much better understanding of menstrual physiology to draw upon, the steady ache sometimes associated with menstruation is attributed to vasoconstriction of the terminal arterioles and consequent tissue ischemia. Since angiospasm is always thought to occur as part of the picture prior to menstruation and endometrial desquamation, even during a nonpainful cycle, this explanation remains incomplete. Yet the mechanism of pain production may be like that which occurs in constricting vascular phenomena and disease of other organs. While angiospasm may well be a basic mechanism responsible for discomfort, the activator again appears to be a hormonal imbalance. Since dysmenorrhea, indeed, since menstruation does not occur in the absence of the female sex hormones, an imbalance of these chemical regulators again appears pertinent.

Our philosophy regarding the cause of primary dysmenorrhea, then, assumes that at least two basic factors are present, (1) myometrial hypercontractility and (2) angiospasm. Both mechanisms reflect a synergistic dysfunction between such hormonal regulators as estrogen and progesterone, on the one hand, and the vascular and myometrial receptors, on the other hand. There are, of course, other concepts concerning the origin of menstrual discomfort which we shall not attempt to discuss here. We do not believe the syndrome of dysmenorrhea to be of single origin. Piecemeal discoveries regarding the physiology of menstruation alter but do not necessarily negate

the possibility that the cramp part of the syndrome is basically of myometrial origin, the steady ache of vascular origin, and that both are the consequences of a transient hormonal imbalance.

A much fuller understanding of blood hormone levels is necessary before these relationships can be finally evaluated. The fact that primary dysmenorrhea tends to disappear with increasing maturity and/or following pregnancy and the birth of a full-term infant lends additional weight to the idea that this transient syndrome is in fact the product of a dysfunctional union between the myometrium, the uterine vascular bed, and their chemical or hormonal regulators. The dual mechanism not only accounts for the variable discomfort characterizing dysmenorrhea but also explains the capricious results obtained with contemporary therapy. All of which brings us to the highly practical matter of treatment.

Management

For those faced with the problem of dysmenorrhea, treatment looms as the most important aspect of this problem, and rightly so. After all, theory will not relieve pain, but it may be the key to the lock. While this is not necessarily true, the theoretical background here presented should help us understand: (a) the failure of therapeutic programs used in the past, (b) the virtues and faults of contemporary treatment, and (c) work yet to be accomplished. Experience has already taught us that it is one thing to know something about the cause of trouble and another thing to correct it. Even when the cause is known, therapy may fall short of its mark. In primary dysmenorrhea, the administration of antispasmodic drugs to control hypercontractility of the uterus and vascular spasm are expected to bring relief. Yet they seldom do so. Perhaps our hope for relief through the use of antispasmodic drugs is neither logical nor realistic. In the first place to depress uterine contractility at its menstrual zenith would probably require a tremendous drug dosage, more, perhaps, than would be good for the individual. Yet, hopefully, we try such therapy only to learn of its futility from the patient. Again, if for the purpose of discussion we agree that the steady-ache portion of the menstrual syndrome is due to angiospasm and its sequelae, by what stretch of imagination have we a right to expect relief from the administration of vasodilator drugs. Not only would such drugs have to be administered *before* the onset of the flow when the angiospasm is at its height but, in addition, the amount would have to be sufficient to overcome the powerful influence of the hormonal chemical regulators causing the vascular and tissue changes. Theoretically, if the dosage were sufficient to do this, the angiospasm, the ischemia, hemorrhage and sloughing of endometrium, in other words, menstruation itself, would not occur. Of course this philosophy is vulnerable in that the "accepted" cause may be incorrect. Even so, let us not be hasty in discarding what today appears to be a logical explanation for menstrual discomfort. Remember, there are to be found in medicine many diseases of known cause with inadequate therapy. While it is desirable that

we try to understand the causes of dysmenorrhea, it is equally important that we recognize the syndrome as a practical problem in pain control. To achieve such control we have a choice of several solutions:

1. Accept temporary disability and resort to bed rest and heat.
2. Give pain-relieving drugs.
3. Prevent or interrupt ovulation.
4. Resort to surgery.

Assuming recognition and treatment of secondary factors which influence discomfort, such as emotional tension, fatigue, ill health, and worry, we may pass on to consideration of the categories mentioned above.

Rest in bed and use of heat are the oldest and commonest remedies for menstrual discomfort. Their usefulness is sometimes overlooked by young male physicians whose knowledge regarding menstruation in general, and dysmenorrhea in particular, is usually tenuous. While suitable for young adolescents not subject to social inconvenience or economic loss, such periodic disablement becomes objectionable or impossible for adults.

The use of a positive pain-relieving drug such as codeine presents several problems. While its employment is widespread, its use is generally preceded by a good deal of bush beating, and sensibly so. Preliminary trial with remedies containing acetyl salicylic acid or Phenacetin in various combinations are to be recommended. They may give adequate relief and circumvent objections accompanying the use of a stronger drug or opiate. When these common remedies fail the use of codeine alone or in combination with stimulants such as caffeine or sedatives such as phenobarbital will serve as an effective means for achieving pain relief. There are, however, several obvious objections to the use of codeine or codeine-containing drugs for this purpose, such as:

1. Their use emphasizes our limited comprehension of the problem.
2. Their use represents palliation rather than cure.
3. The nausea and vomiting, sometimes a part of the dysmenorrhea syndrome, may interfere with desirable oral administration.
4. Gastrointestinal irritation sometimes caused by the drug itself may prove objectionable.
5. The sinister allusion to habituation which hovers over the use of codeine makes us reluctant to prescribe it.

Despite the commonplace use of the hypodermic syringe for a wide variety of therapeutic purposes without evidence of physical harm or moral disintegration, in this instance we favor the oral use of codeine, not only because this is more convenient, but also because it is psychically better for the patient and ethically less disparaging to the medical profession. While codeine should not be prescribed unless necessary, we believe the hazard of habituation to be negligible from the monthly use of small amounts for the relief of incapacitating dysmenorrhea.

Since primary dysmenorrhea does not occur in the absence of ovulation the prevention of ovulation by the administration of adequate amounts of estrogen or testosterone during the first half of the cycle represents a positive method for providing relief. However, this method also has its limitations. It is probably unwise to prevent ovulation for many months in succession. Perhaps this caution is unnecessary. Possibly time and experience will reveal that ovulation may be inhibited for months without harm to the patient or

interference with the return of ovulation when this is deemed desirable. Until we can be assured regarding these points, however, this method should be utilized for restricted periods of time only. Use of the male hormone to prevent ovulation has the added objection that in some instances its use causes hirsutism and occasional voice changes. While these manifestations commonly disappear upon discontinuance of the drug, they do not always do so.

The surgical management of primary dysmenorrhea is generally limited to (1) thorough dilatation of the cervix and currettage of the uterine cavity, or (2) presacral neurectomy. While both these surgical procedures have a place in our therapeutic armamentarium they are to be looked upon as last-resort measures. The complete relief which has sometimes been achieved by surgery has led some patients as well as physicians to decry what, in the name of caution, appears to have been an unnecessary and avoidable delay in resorting to surgery. However, the indications for surgery can be established only after time has permitted a thorough attempt at relief by other methods and has adequately proved their failure. Furthermore, primary dysmenorrhea is commonly a self-limiting disease and the immediate need is principally that of palliation. It is not like some secondary dysmenorrheas which become progressively worse with advance of the causative disease and invariably require surgical interference.

While there is nothing new in these suggestions for treatment, we have stripped management of much of the fanfare and window dressing with which it is commonly accoutered. Anyone following the principles here outlined will have a reasonable grasp of the problem presented by primary dysmenorrhea and specific, usable relief-giving suggestions for its control.

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Discussion

DR. ROBERT A. KIMBROUGH, Philadelphia, Pa.—It is very important that these girls be encouraged to go out and participate in sports. Acrobatic dancing distracts attention from menstrual pain which they have nourished and clutched to their bosoms, expecting it to come, month after month. I have never seen really crippling dysmenorrhea of primary type in a girl who was well adjusted emotionally.

DR. A. F. LASH, Chicago, Ill.—First, I wish to know why dilatation of the cervix gave such relief. Second, we do not find that all our women who have presacral neurectomies gain relief. Has Dr. Miller had any experience with Donald's resection of the ovarian nerves?

It is a little disconcerting to a patient to have an operation for dysmenorrhea, and then subsequently have the same trouble.

I find that I have become much more effective in my therapy as I have grown older, since I am more confident of the fact that the patient has no pathology present, and I am able to impress her with that fact.

I think we receive a good bit of information from the various girls' schools. At the beginning of the year, about 90 per cent of the girls have dysmenorrhea, but, as a result of regular diet, proper hours, good exercise, and peace of mind, we find that by June the incidence of dysmenorrhea drops down to about 20 per cent. I think the 20 per cent can be dealt with by the gynecologist, exercising his small knowledge of psychiatry, and not by professional psychiatrist. I think to a great degree we can convince the girl—without the presence of her mother—that nothing is wrong with her, and most of the pain of dysmenorrhea then disappears.

If the condition persists in spite of these simple measures, I usually find there is a disturbed mental condition.

DR. EMERSON K. BLEWETT, Austin, Texas.—I think that more important than the division of dysmenorrhea into the primary and secondary varieties is the division according to the severity of the pain with the menstrual periods. The reason that a patient with severe dysmenorrhea consults the doctor is that she has been unable to adjust her life adequately to one to three days of disabling pain each month. Very frequently these girls seem to show an immature type of personality.

The psychologic factor so often mentioned in the literature as the cause of dysmenorrhea is likely to be the result rather than the cause of the pain.

To obtain the confidence of these girls, as well as to give them some confidence in themselves, a guarantee of menses free from pain may be the first step toward a better adjustment. Without such confidence, all these general measures that have been mentioned and have been found to be helpful in the past, such as diet, routine habits, and exercises, are likely to be of no avail.

Every investigator must realize the tremendous psychologic influence of evaluating the subjective symptoms of pain, and he must make every effort to have as much objectivity as possible.

Almost any type of therapy, even with apparently inadequate control, has been shown to be successful in a majority of patients in almost any series which you might study.

It is believed that suggestion, either consciously or unconsciously, enters into the treatment of many cases of dysmenorrhea, since the percentage of cases improved, as reported from either scientific or unscientific sources, averages about the same, except those cases treated by (1) castration, (2) presacral neurectomy, or (3) suppression of ovulation.

Dr. Miller mentioned the recent work of Wilson and Kurzrok, and Bickers and Torpin, who, with the use of small sterile intrauterine rubber balloons, recording on a kymograph, studied intrauterine pressure changes at different times in the menstrual cycles in human subjects. In women menstruating normally and regularly, as judged by the regularity and amount of the flow, they found that, 4 to 7 days following a period, small, rapid uterine contractions commenced, and persisted for 10 to 14 days. Following this so-called follicular phase, contractions of a deeper amplitude and longer duration appeared. These contractions of the luteal phase increased in amplitude, and reached maximum height on the first two days of the menses.

According to Kurzrok, these intrauterine pressure changes in women with primary dysmenorrhea are the same as in women with normal menstruation.

We do not know what the trigger mechanism is. However, in an anovulatory cycle, as demonstrated by endometrial biopsy, there is a complete lack of these larger, less frequent contractions of the luteal phase, and a prolongation of the smaller, more rapid contraction of the follicular phase throughout the period.

Dysmenorrhea has been found to occur only in the presence of a normal functional corpus luteum and the normal endometrial cycle. The absence of dysmenorrhea in the anovulatory cycles is attributed to the absence of the large luteal-phase contractions, and, in all probability, painful menstruation is the result of abnormal physiology in the myometrium, and is not related to any endocrine changes.

Suppression of ovulation by large doses of oral estrogens, for the relief of dysmenorrhea, has been reported by numerous investigators, with excellent results. In the past four years I have used this form of therapy on 75 patients with severe dysmenorrhea, either secondary or primary. These 75 patients were from a group of 210 gynecological patients who complained of dysmenorrhea of varying degrees of severity.

A conjugated estrogen such as Premarin—7.5 mg. daily for 20 days, beginning with the third day of the menses—is the therapy recommended for the first few cycles. Conjugated estrogens are well tolerated by the patient, and lack the toxic effects so frequently seen in the use of synthetic estrogen-like drugs. Seventy-three of these patients obtained complete relief from pain on this therapy. Two patients, not relieved, were cured by cycle therapy.

DR. WILLIS E. BROWN, Little Rock, Ark.—It might be worth while to carry the discussion one step further, with perhaps an explanation of why this is a self-limiting disease. Again, if I may call upon my own philosophy, it is our interpretation that the maturing aspect and the increased vascular aspect of gestation are perhaps the features which tend to terminate this process, rather than the obvious dilatation of the cervix.

I find difficulty in accepting the concept of cervical stenosis as a basic problem in dysmenorrhea, and much prefer to accept the philosophy which Dr. Miller has suggested, namely, that it is an ischemic uterine contraction which causes the discomfort, and that from this ischemic uterine contraction and cramps we then have ramifications throughout the rest of the sympathetic nervous system manifesting themselves in nausea, vomiting, sweating, and other psychosomatic manifestations.

One problem which has come to my attention, which may come to yours, is that while we can cause a relief of pain by the suppression of ovulation, by any of a large variety of techniques, we have been unable to accomplish this consistently month after month, in essentially normal women. While it may work very well for the first month, and you can relieve a patient of her dysmenorrhea by stopping ovulation for a month, as you continue the schedule into the second and third and fourth months, in my experience, it breaks down and ovulation occurs, perhaps by an adjustment mechanism.

I would be interested to know whether Dr. Miller and his associates have any explanation as to why we are unable to continue this form of relatively satisfactory therapy on a more long-term basis.

I should also like to add one other comment. Just as no two feet and shoes are alike, so no two dysmenorrheas are alike, and I think it is somewhat fallacious for us—in our striving at accumulation of scientific data—to put all of our dysmenorrheas into one category and to utilize one schedule of therapy. To be sure, it does add to the value of your statistical data. On the other hand, some patients are better served by one form of therapy than another, and I would like to suggest that you try several forms of therapy before abandoning medical care for the more radical forms of surgical resection.

At times an ovulation can be produced by male hormone better than by female hormone; at times one sedative is better than another; at times different psychotherapeutic approaches are more satisfactory. And if you will try a variety of techniques for these patients, perhaps by the simple clinical expedience of trial and error (which is quite unscientific, but very therapeutically useful) you may relieve many of these patients.

DR. ARTHUR G. KING, Cincinnati, Ohio.—I do not think there is any question but that the contractions of the uterus are involved in dysmenorrhea. However, why is it that during pregnancy the sometimes rather powerful Braxton-Hicks contractions, while they are perceptible, are not painful?

We have many cases of false labor, near term, without any particular effect, of course, but then at term there are myometrial contractions, which become painful. I think most of the women are able to count to 9 months, and I am wondering what part that plays in the perception on the part of the woman of her myometrial function.

During the war, in the South Pacific, I had the unusual opportunity of doing a good deal of work with natives. We found that, periodically, some of the native women (who had been brought over from a distant island to work) presented themselves at our clinics, and since we could not get together on language, the diagnosis was made purely on objective observations. We almost always found that these women were suffering from whatever it was that they complained of at the menstrual period. Almost invariably, they were menstruating when they presented themselves to us.

I had occasion to go to an uncivilized island, and to live there for three days among the natives. I made as many observations as I could, and found that a very ancient Biblical custom was being observed, namely, that when a woman started to menstruate she left the tribe (the tribes had a population of 60 or 100 at the most), went downstream about half a mile to a little hut which was reserved for such purposes, and waited out her three or four days.

Through interpreters I was able to make very definite inquiries about dysmenorrhea. These women never had dysmenorrhea, or certainly never complained of dysmenorrhea when they were in this little hut, a half mile from anyone else in the tribe. Usually there was not even another woman there, unless by coincidence two women happened to be there at the same time.

I wonder what part the element of tension—in a very deep and completely unconscious way—has in causing dysmenorrhea. I heartily agree with Dr. Lash that the point of emphasis should be on the mother rather than the young girl.

DR. F. J. HOFMEISTER, Milwaukee, Wis.—After we have removed the words *curse* and *sick time* from the vocabulary of the young girl, as early as possible, and after we have tried to psychoanalyze her and use psychosomatic methods on her, after we have created the anovulatory cycles with some success, or with great success, or with no success, I am concerned with one thing—the fact that we see so many girls who are left not cured.

There is no question in the mind of the physician but that the patient who has a frankly diseased pelvis needs attention, but there are ever so many women with early endometriosis who have inadequate diagnoses, who are still being laughed at because, in many instances—I believe, from my limited experience—endometriosis can be of a minor degree with a great number of symptoms. Conversely, the patient can have a pelvis full of endometriosis with no symptoms, and I am concerned about these patients who, month after month, are treated psychologically, treated with stilbestrol, treated with psychoanalysis, and then finally some doctor does a rectovaginal examination, and has knowledge enough to make a diagnosis of early endometriosis. This diagnosis and explanation may be therapeutically effective in this condition.

DR. MILLER (Closing).—I quite agree with Dr. Kimbrough's observation that when you have pain you are uncomfortable. As physicians, it is our job to find out why menstrual discomfort occurs, and do something about it. Shoes can be removed but to remove the uterus is not quite so feasible.

I never hear the statement about checking up on the mother's attitude regarding dysmenorrhea and the emphasis placed on the psychic aspects, without also being impressed by the fact that we men (I think there are one or two women in the audience) talk glibly about dysmenorrhea, yet none of us ever had it. We pretend to know something about it and how to treat it. We look wise when patients consult us, yet not one of us has ever felt the discomfort of dysmenorrhea.

We agree that there is such a thing as a low pain threshold. Some individuals tolerate discomfort less well than others. We also agree that many times emotional factors, such as have been emphasized here by a number of discussants, constitute a very important factor, and may sometimes actually assume an etiological role in dysmenorrhea. If ovulation is prevented by appropriate therapy and we prove the presence of an anovulatory cycle by endometrial biopsy in a patient who still complains of pain, despite the fact that the ovulation was prevented, we may then assume, perhaps, that we are dealing

with a functional type that may benefit by attention from the psychiatric point of view. However, we believe that the number of individuals who have dysmenorrhea on the basis of a pure psychogenesis or functional basis is not great.

Most young women are healthy and more mature than we sometimes appreciate.

Dr. Lash commented on presacral neurectomy, and the wisdom of cutting the ovarian nerve. I cannot say much about the latter since our experience with this procedure is limited. I have wondered whether it makes much, if any, difference in the results following presacral neurectomy, whether or not the infundibulopelvic ligament is cut. More likely the failures in presacral neurectomy are due to an inadequate operation or unwise choice of patient and treatment.

Prevention of ovulation—to see whether the patient is relieved—should certainly be undertaken before presacral neurectomy is considered.

Dr. Blewett commented on the severity of the pain as the important thing. If the patient is uncomfortable, regardless of the cause, we should find some way of providing immediate relief, and then do something about preventing or controlling the condition in the future.

Dr. Brown commented on the maturing aspect and increased vascularity as a factor that may lead to ultimate relief. He pointed out that permanent relief from the use of hormones in preventing ovulation does not occur. Anyone who has used this method to control dysmenorrhea has doubtless noted its gradual loss of effectiveness. This may be due to immunization, if you wish, or possibly the patient develops a certain amount of resistance to this method of palliation.

Dr. King commented on Braxton-Hicks contractions and false labor pains. He asked why, if uterine hypercontractility is a factor in the causation of menstrual discomfort, the patient who has Braxton-Hicks contractions does not also have an equal amount of discomfort. I would say that the answer to this question has been very adequately demonstrated in that the pressures produced and the severity of the contractions in dysmenorrhea are many times greater than the intrauterine pressure occurring during normal labor.

Dr. King also emphasized the importance of the "mother factor" in dysmenorrhea, which I think is all right, but some mothers are very sensible. Remember, the mothers of today were the young women of 25 years ago, when a healthy, physiologic attitude toward menstruation began to be widely emphasized. Generally speaking, they have instilled a lot of good common sense into their daughters.

There certainly can be no argument with Dr. Hofmeister's comments regarding endometriosis as a contributory factor in some unexplained cases of severe dysmenorrhea. However, one must always keep in mind that even with extensive endometriosis more than 50 per cent of the patients will have no pain, so we cannot conclude that, because the patient has severe unexplained menstrual cramps, she has hidden endometriosis.

TOTAL HYSTERECTOMY AT CESAREAN SECTION AND IN THE IMMEDIATE PUERPERAL PERIOD*

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ON OCT. 19, 1948, a 33-year-old Negro woman, gravida x, para viii, was delivered spontaneously on the Tulane Obstetrical Service at Charity Hospital. Two hours later it was discovered that she had suffered a rupture in the lower uterine segment, and immediate laparotomy was performed. An intramural fibroid was discovered under the bladder flap, in the anterior portion of the lower uterine segment from which the tear originated. This was felt at the time to have been contributory.

A subtotal hysterectomy was planned but after amputation of the body of the uterus, bleeding continued from the cervical stump in an area wherein the rupture extended. Ultimately it was necessary to remove the cervix completely. This, to our knowledge, was the first total hysterectomy to have been performed at or post delivery on our Service or at Charity Hospital. The obstetricians were V. A. Davidson and Frank Nix. The patient's postoperative course was uneventful.

In May, 1949, one of us (F. N.) was confronted with a similar situation occasioned by a placenta previa accreta. On this occasion he devised an original technique to facilitate removal of the cervix which has become a facile and standard procedure used to date.

This report is concerned with an analysis of total hysterectomy at cesarean section or in the immediate puerperium.

Material

The material was collected from case reports from the Tulane Obstetrical Services at Charity Hospital in New Orleans and Pineville, La., and from private patients at the Ochsner Clinic. All but one occurred from Jan. 1, 1949, to Oct. 1, 1952.

In order to justify a series of this magnitude over a relatively short period of time, it is interesting to note the general problem of cesarean section on the Charity Hospital service in New Orleans. It represents a rather constant trend which has varied little from year to year or for the period of this study.

From Jan. 1, 1949, to Jan. 1, 1952, there were 43,007 deliveries on all services at Charity Hospital (Table I). Of these 1,105 were delivered by cesarean section, a rate of 2.56 per cent. On our service there were 12,095

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**Ochsner Clinic.

TABLE I. DELIVERIES AND CESAREAN SECTIONS, JAN. 1, 1949, TO JAN. 1, 1952

	DELIVERIES	CESAREAN SECTION	
		NUMBER	RATE %
Charity Hospital	43,007	1,105	2.56
Tulane Service	12,095	450	3.72

deliveries and 450 cesarean sections, a rate of 3.72 per cent. One then can see that although the rate of cesarean section is relatively low, the total number would present many opportunities for decision for hysterectomy in those patients who have reached a section saturation point. Again, since the total number of patients includes some 80 per cent Negroes, the high incidence of uterine fibroids (and often degenerating fibroids), as well as complications of pregnancy in this race, would present many occasions when hysterectomy was advisable.

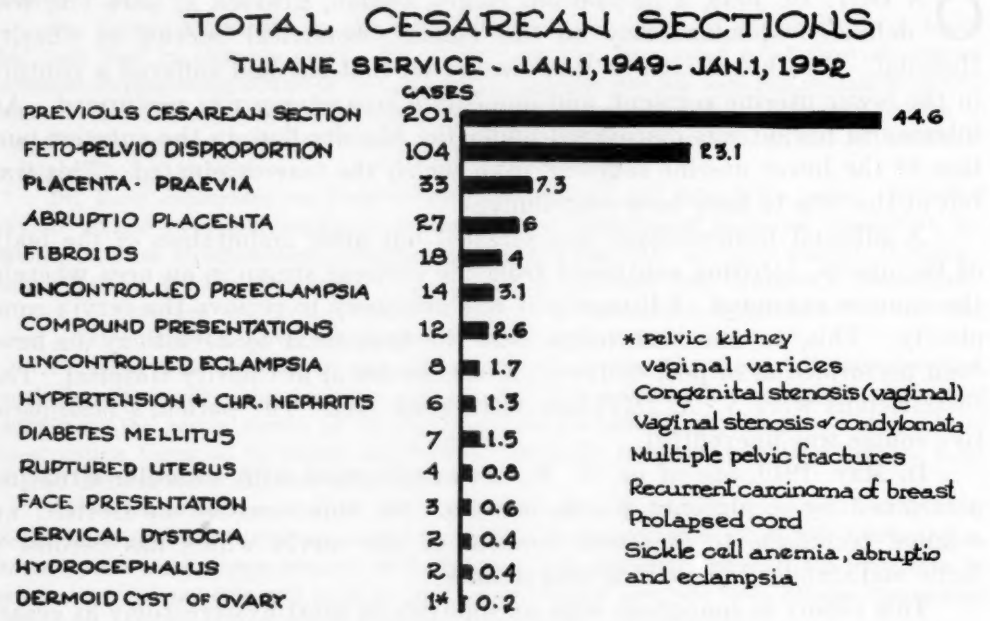

Fig. 1.

Of the total indications for cesarean section, 44.6 per cent were repeat procedures (Fig. 1) and 23.1 per cent for disproportions (for the most part contracted pelves). These two prominent indications, combined with the high toxemia incidence, abruptio placentae, placenta previa, and uterine fibroids, comprise 89.8 per cent of the indications for cesarean section. In many of these women hysterectomy becomes indicated. There is in addition the constant flow of emergency situations: neglected compound presentations with intrapartum sepsis, ruptured uteri on admission, and long-standing massive placental separation, which often require immediate hysterectomy in order to preserve the life of the mother.

Including the first patient in 1948 there were 75 total hysterectomies at or post delivery performed on the Tulane Obstetrical Service from Jan. 1, 1949, to Oct. 1, 1952. There were 10 performed at the Ochsner Clinic, all following cesarean section. There were 64 Negro and 21 white patients, their ages ranging from 20 to 45 years (Fig. 2). Parity ranged from zero to fifteen; eleven

TABLE II. AGE AND PARITY

AGE (YEARS)	PARA 0	i	ii	iii	iv	v	vi	vii	viii+	TOTAL
20-25	1	2	12	6	2	1				24
26-30			7	2	3		1		1	14
31-35	2	1	2	5	2	1	1	4	2	20
36-40	1	3	5	4	1		1	1	5	21
41-45		1	1	1					3	6
Total	4	7	27	18	8	2	3	5	11	85

women had had 8 or more babies, and six had had 11 or more (Table II). In the 20 to 25 year age group, of 24 patients, 21 had had 2 or more previous babies and 8 had had 3 or more. It was in this young group that repeated section (80 per cent), toxemia with abruptio placentae, ruptured uteri, and placenta accreta were responsible for the indications.

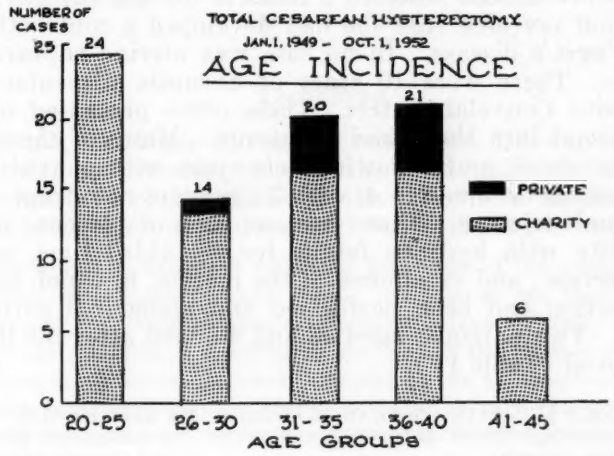

Fig. 2.

Indications

We divide the indications for hysterectomy into two main groups, one, those elective procedures which are concerned with the patient who has repeated cesarean sections and whose uterus, in the conscientious opinion of the operator, should or would not support another pregnancy, the other, situations which demand hysterectomy to preserve the life or the future welfare of the mother. The last are usually emergencies.

TABLE III. TOTAL CESAREAN HYSTERECTOMY

Previous Section.—		
None	34	
1	16	
2	21	
3	6	
	—	
		77
Total Hysterectomy Post Partum.—		
Uterine rupture	5	
Placenta accreta	2	
Couvelaire uterus	1	
	—	
		8
Total		85

In this study there were 77 women who had total cesarean hysterectomies. Of these, 34 followed primary section; 16 one previous, 21 two previous, and 6 three previous sections (Table III). There were 8 total hysterectomies performed post partum for uterine rupture, placenta accreta, or Couvelaire uterus.

For comparison, the indications for the Charity and private groups are analyzed separately. Of 75 on the Tulane Obstetrical Service, 8 were performed post partum. Of the remaining 67, there were 32 primary and 35 secondary cesarean section hysterectomies.

Primary Section.—

There were 7 instances of uterine fibroids, in 1 degenerating fibroids, and in 3 a transverse lie as well. Six women had ruptured uteri, 4 on admission. Two ruptured in the course of labor. One of these patients was a 34-year-old gravida ix, para viii, who had no previous obstetrical difficulty and who had delivered without incident her last baby (7 pounds, 7 ounces) four years previously on our service. She suffered a massive uterine rupture. Postpartum x-ray investigation revealed that she had developed a contraction of the pelvic inlet with Paget's disease. In no case was uterine rupture preceded by cesarean section. There were 10 cases of abruptio placentae all of which resulted in massive Couvelaire uteri. These often presented in addition extravasation of blood into the broad ligaments. Many of these women have been admitted in shock and following eclampsia with convulsions at home. Uncontrolled toxemia occurred in 4, with 3 instances of intrapartum infection and one of vaginal stricture. There was one each of placenta previa accreta; Rh incompatibility with hydrops fetalis for the third time, combined with intrapartum infection; and carcinoma of the rectum, in which patient a transverse colon resection had been performed and abdominal perineal resection was anticipated. Two patients, aged 38 and 40, bled after the infant and placenta were removed (Table IV).

TABLE IV. INDICATIONS IN 32 CASES OF PRIMARY SECTION

FOR SECTION		FOR HYSTERECTOMY	
Uterine fibroids	4	Degenerative fibroids	1
		Multiple fibroids	3
Transverse lie	3	Multiple fibroids	3
Rupture of uterus	6	Rupture of uterus	6
Abruptio placentae	10	Couvelaire uterus	10
Uncontrolled toxemia	4	Intrapartum infection	3
		Vaginal stricture	1
Placenta previa	1	Placenta previa accreta	1
Rh incompatibility Hydrops 3 times	1	Intrapartum infection	1
25 year sterility in 40-year-old patient	1	Postpartum hemorrhage	2
Repaired 16 year fistula in 38-year-old patient	1		
Carcinoma rectum (colectomy)	1	Perineal resection to follow	1

Repeat Section.—

In patients who had had previous cesarean sections (35), the indications for these are listed. Removal of the uterus was felt justifiable because of the condition of the uterine scar in 23, for fibroids in 8, for hemorrhage in 2, and for silent rupture in 2 (Table V).

Of the 10 private patients, 8 had repeat cesarean sections. Of these there were additional findings of uterine fibroids in 3, toxemia in 3, and in 1 tuberculosis and previous thoracoplasty. The two primary sections were performed for abruptio placentae and uterine fibroids.

As to absolute indication for total hysterectomy, there was no departure from previous thought whenever the subtotal or Porro section was indicated. We have striven to avoid the pressure from either sentiment, economic or eugenic sources, hence the element of pure sterilization occurred infrequently.

TABLE V. INDICATIONS IN 35 CASES OF REPEAT SECTION (ONE OR MORE)

FOR PRIMARY SECTION		FOR HYSTERECTOMY	
Disproportion	25	Uterine scar	18
		Uterine fibroids	3
		Postpartum hemorrhage	2
		Silent rupture	2
Uterine fibroids	2	Degenerating fibroids	1
		Multiple fibroids	1
Abruptio placentae	2	Uterine scar	2
Placenta previa	4	Uterine scar	2
		Uterine fibroids	2
Uncontrolled pre-eclampsia	1	Uterine fibroids	1
Poliomyelitis	1	Uterine scar	1

Technique

At Tulane the technique developed will allow the experienced operator to perform a total hysterectomy within the time limits of the usual cesarean section. This has proved beneficial to the patient in instances of ruptured uterus, massive concealed abruption, and other shock-producing causes.

Step I.—The infant is delivered following dissection of the bladder flap downward, through a low transverse incision in the uterus. As soon as the fetal head is delivered, the mother receives 1 c.c. of ergonovine or Methergine intravenously. If early placental separation occurs, the placenta is removed; if not, and in the absence of uterine bleeding, however, immediate steps are made toward completing the hysterectomy. An O'Sullivan-O'Connor retractor is inserted and the uterus delivered through the wound. On each side in turn, the round ligaments are clamped and cut, the broad ligaments then clamped in one or two bites depending on the anatomy and cut. The uterine vessels are identified, double clamped, and cut. At this stage, then, the uterine bleeding is controlled for the most part. The uterus, already one-half amputated by the transverse incision, is completely amputated by continuing this incision posteriorly, after a transverse incision in the posterior peritoneum, and slight peritoneal dissection toward the uterosacral ligaments. To this point the procedure can be done in a matter of a minute or two, particularly if an operator on each side does his own side. The cervix is held together with two sponge forceps. Sutures are now applied to the round and broad ligaments by fixation. The uterine vessels are tied by a single suture.

Step II.—The cardinal ligaments are now clamped and cut on each side and their suture reties the uterine vessels on each side. A finger is then introduced through the cervix and brought upward, posteriorly, between the uterosacral ligaments. The junction of the soft, often hard-to-identify cervix and the vagina is thus found and an incision is made from the abdominal side over the inserted finger. The vagina is thus entered and by circumcision the cervix is removed. In this fashion even a completely dilated cervix is discernible and the integrity and length of the vagina unimpaired. Naturally, if the cervix is long, closed, and easily identified, it is unnecessary to utilize this point of technique.

Step III.—Gloves are then changed. The vaginal cuff is sutured with running chromic No. 1 catgut. The angles then are sutured with a purse-string suture which includes, in turn, the angle of the cuff, the uterosacral ligament, round ligament, shelf of the broad ligament (infundibulopelvic) and the bladder. These two almost completely reperitonize the cuff. Continued peritonization is then accomplished.

Oophorectomy is performed only if there exists ovarian disease regardless of age.

Surgical Complications

Of the 85 cases, 73 (85.9 per cent) were uncomplicated (Fig. 3). Seven patients exhibited shock, 2 hemorrhage, 1 spinal shock, and 2 marked afibrinogenemia in instances of abruptio placentae.

The anesthesia employed was spinal in 54, general in 29, and local infiltration in 2.

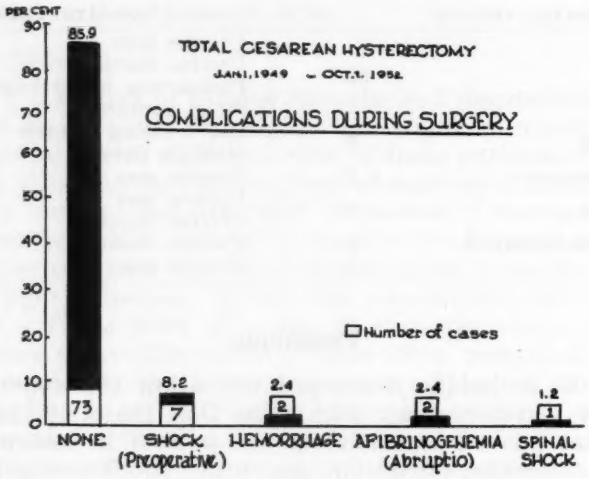

Fig. 3.

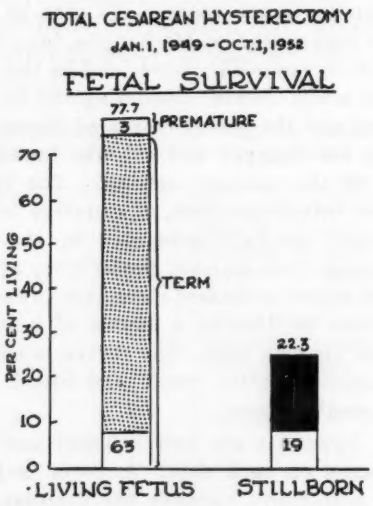

Fig. 4.

Postoperative Complications

Fifty-five patients exhibted no postoperative complications. Of those considered to have complications (Table VI) there were 7 cases of atelectasis, 7 urinary infections, 5 instances of shock, 6 of mild ileus, 2 pelvic hematomas of minor degree, 3 instances of anuria, 4 of pertionitis, 4 of pneumonitis, and one each of cuff hemorrhage, transfusion reaction, acute cholecystitis, and cerebral thrombosis. The hospital stay for 54 women was 8 days (Table VII). In the majority of cases (75) it was 11 days or less; the longest hospital stay was 23 days in one instance. Four women were discharged on the seventh postoperative day.

TABLE VI. POSTOPERATIVE COMPLICATIONS

None	55
Atelectasis	7
Urinary tract infection	7
Shock	5
Ileus	6
Pelvic hematoma	2
Anuria	3
Peritonitis	4
Pneumonitis	4
Wound suppuration	1
Cuff hemorrhage	1
Transfusion reaction	1
Acute cholecystitis	1
Cerebral thrombosis	1

TABLE VII. HOSPITAL PERIOD

NO. OF DAYS	NO. OF PATIENTS	
7	4	
8	54	
9	4	
10	7	
11	6	
12	2	
13	1	
15	2	
18	1	
19	1	
23	1	2 Deaths
Total	83	

Morbidity and Mortality

Fifty-five patients, 64.7 per cent, were nonmorbid (Table VIII), thirty, 35.3 per cent, exhibited fever of 100.4° F. for one or more days, and seven, 8.2 per cent, morbidity for three or more days.

TABLE VIII. MORBIDITY

NO. OF DAYS	NO. OF PATIENTS	PER CENT MORBIDITY	
0	55		None
1	12	27.1	
2	11		
3	2		35.3
4	2	8.2	100.4° F.
5	2		
8	1		
Total	85		

There were 63 term live babies, 3 live prematures, and 19 stillbirths (22.3 per cent), as shown in Fig. 4. The cause of intrauterine death was uterine rupture in 7 cases, massive abruptio placentae in 10, erythroblastosis in 1, and transverse lie with prolapsed arm and intrapartum infection in 1.

There were 2 maternal deaths, an incidence of 2.35 per cent. Both were on the Tulane Obstetrical Services and the causes of death were incidental to the procedure. One patient, a 28-year-old gravida iii, para ii, Negro woman, was admitted on Dec. 31, 1951. She was delivered on Jan. 1, 1952, at 8 P.M. following a prolonged labor of 24 hours. A moderately difficult forceps delivery was performed following which the uterus was found to have ruptured. At laparotomy it was the opinion of the obstetrician that a generalized peritonitis of relatively long standing was present. She died of overwhelming sepsis the following day.

The other, a 20-year-old Negro woman, gravida i, para 0, was admitted following multiple eclamptic convulsions at home. There were no fetal heart tones and the cervix was closed. The eclampsia was controlled and in 24 hours a concealed abruptio placentae was suspected. Anuria developed and when delivery from below seemed not forthcoming a laparotomy was performed. A Couvelaire uterus was discovered together with massive hemorrhage into both broad ligaments. Following hysterectomy she recovered, overcame a lower nephron nephrosis, and was observed to improve. However, on the twentieth postoperative day she suddenly died of what was diagnosed as a cerebral thrombosis. Autopsy was denied.

Comment

Experience has proved so far that, in addition to the widening of the indications for cesarean section and the lowering of maternal risk with modern surgery in trained hands, obstetricians are faced with the ever-present problem of the patient who has reached the threshold of safety for future pregnancies. These women, to be protected, must submit to tubal sterilization, their husbands to vas ligation, contraception, or the practice of abstinence. There are numerous objections both from the standpoint of abhorrence in a few, to a legitimate conviction of flagrant violation of the moral code in many. Tubal ligation in itself has not positively protected every patient from future pregnancy. Failures have continued to present themselves.

In these patients we have accepted the line of thought that the uterus itself becomes the diseased organ. If this observation is conscientiously made, then by logic there is justification for its removal. This judgment should not be influenced by the number of previous cesarean sections, by sentimental, economic, or eugenic reasons. One then acts within the limits of clear scientific principles which are basically moral.

In the problem of the woman with multiple uterine fibroids and degenerating fibroids, judgment should be the same as that for the nonpregnant uterus. Age, in some few instances, can find justification, particularly in the face of severe cardiorenal and/or toxic disease.

The emergency situations speak for themselves. This is particularly true of massive uterine rupture, and in our experience acute massive, often concealed, abruptio placentae. Prior to the radical approach to the last category, attempted conservatism was responsible for 60 per cent of the maternal deaths on the service in 1949. All four women had concealed hemorrhage, were admitted with dead fetuses, and died of the sequelae of shock, anoxia, or afibrinogenemia. These were the women who later exhibited lower nephron nephrosis or pituitary necrosis. Certainly, then, early emptying of the uterus is indicated, and if this cannot be accomplished within a short period of time via the vagina then the abdominal route is the conservative one so far as maternal welfare is concerned. Although many uteri exhibiting intramural and/or subserosal extravasation of blood are left in situ, the massive Couvelaire uterus which fails to react to oxytocic drugs should be removed.

Most of us are in agreement that removal of the cervix at hysterectomy is a sound procedure and of maximum benefit to the patient. In parturient women this has been avoided because of the fear of increasing operative time, provoking bleeding, and/or shortening the vagina. This has not been our experience. The shortest operative time was 32 minutes, the average 1 hour, 15 minutes, and this, for the most part, in the hands of residents in training. The technique described minimizes bleeding. The method described to search for the cervical vaginal junction in partial or completely dilated cervices assures removal of the cervix at the proper level and postpartum normal vaginal depth with proper support has been the universal finding. In many respects

we are in agreement with Davis,[1] whose experience in "100 complete cesarean hysterectomies" parallels this report.

The present trend, then, as far as we are concerned, is to replace the subtotal procedure with the total or complete cesarean hysterectomy (Fig. 5).

Finally, we are all in agreement at Tulane that whenever there exist indications for uterine removal, the entire uterus must be removed whenever possible. This can be accomplished safely and with facility in trained hands.

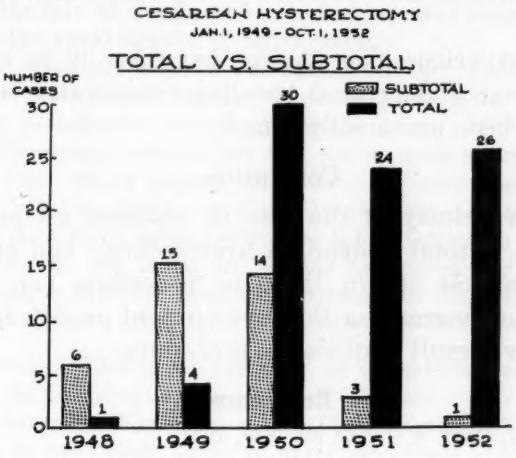

Fig. 5.

Summary

1. Eighty-five total hysterectomies at cesarean section or post delivery are herewith presented. Ten are from private practice, and 75 are from the Tulane Obstetrical Services.

2. Although the total number were collected within a three and one-half year period, they represent a small percentage of the total number of cesarean sections performed (150 per year). The present section rate is 3.72 per cent (Tulane).

3. Approximately 44 per cent of the sections are repeat sections and 23 per cent are for disproportion. These added to the relative high incidence of toxemia, fibroids, and abruptio placentae in the Negroes (80 per cent of total deliveries) will eventually produce many women in whom hysterectomy is indicated.

4. The indications for total hysterectomy at cesarean section or in the immediate puerperium are the same as for the subtotal or Porro section.

5. The uterus is amputated above the cervix and the technique for removal of the cervix is described.

6. There were no surgical complications in 73 patients. Seven exhibited shock, 2 hemorrhage, 2 afibrinogenemia, and 1 spinal shock.

7. Postoperative complications were observed in 30 cases consisting of atelectasis (mild), mild ileus, urinary tract infection, and shock. There were two pelvic hematomas of minor degree, 1 cuff hemorrhage, 3 instances of anuria, and 1 of abdominal wound separation.

8. Thirty patients were morbid for 1 or more days (35.3 per cent) and 7 for 3 or more days (8.2 per cent).

9. There were 19 stillbirths, 7 of which occurred in ruptured uteri, 10 from abruptio, 1 from erythroblastosis, and 1 from neglected transverse lie, a rate of 22.3 per cent.

10. Two maternal deaths (2.35 per cent) were incidental to the procedure. One of these mothers had long-standing pertionitis associated with uterine rupture, and the other, with eclampsia, abruptio, Couvelaire uterus, and lower nephron nephrosis, died on the twentieth postoperative day of a cerebral thrombosis.

11. Operative experience has shown that there is no cause to leave the cervix in situ for fear of increased bleeding or operative time. Postpartum vaginal support has been universally sound.

Conclusion

Whenever hysterectomy at the time of cesarean section or in the puerperium is indicated, a total abdominal hysterectomy can and should be performed. Experience has shown that the procedure can be performed in trained hands without increasing the time element or risk to the patient, and that the postoperative result justifies the procedure.

Reference

1. Davis, M. E.: Am. J. Obst. & Gynec. 62: 838, 1951.

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Discussion

DR. RONALD R. GREENE, Chicago, Ill.—I come from an institution where we are very liberal with the performing of cesarean total hysterectomy, principally for the purpose of sterilization in a patient who is properly prepared psychologically. She must know that menstruation is not a necessity, and that the function of the uterus is to have babies, and that is its only function. If the patient does not agree with this, of course, I think doing a total hysterectomy is a grievous sin.

The question has been raised by Dr. Galloway—by implication, at least—as to the relative danger of doing a cesarean hysterectomy for sterilization purposes, compared to tying the tubes. Of course, I just—coincidentally—had some figures in my back pocket.

Dr. Joe Chung has just finished going over the data for the last six years at Wesley Memorial Hospital in Chicago. Fifty-four cesarean hysterectomies were done in a total of 759 cesarean sections. There is a difference between an elective cesarean hysterectomy that is done on purpose and one that is done because of infection, or a ruptured uterus or Couvelaire uterus that keeps on bleeding. In these latter instances the total hysterectomy is done as a lifesaving procedure in a patient who is already in shock or potentially in shock.

The figures were divided up into elective cesarean hysterectomies and nonelective hysterectomies. There were 31 in the elective group and 23 in the nonelective.

The data obtained from these were compared with those of elective and nonelective cesarean sections performed during the same period of time.

Dr. Chung will eventually publish these findings. There were, however, no significant differences in the morbidity, complications, and length of hospital stay between the elective cesarean sections and elective cesarean hysterectomies. Approximately one-half of the cesarean hysterectomies were done by the resident staff. We do not consider it to be a particularly difficult operation. It is a safe and certainly the most effective form of sterilization.

DR. HUGH HAMILTON, Kansas City, Missouri.—We agree that the total hysterectomy should be the method of choice. I liked the indications given. I am a bit dubious about the tuberculosis indication, unless it is a very advanced and very serious case.

However, we branched off into a philosophical point in this discussion, and that is the one as to the use of hysterectomy for purposes of sterilization. If we are going to sterilize, let's be honest and say we're sterilizing, and do a sterilizing procedure. Let's not hide behind something. I do not approve of hiding behind the removal of the uterus, for the simple purpose of sterilization. If you are going to sterilize, stick your chin out and say, "I'm sterilizing."

DR. JOHN C. WEED, New Orleans, La.—I rise to bring up but one point, and that is a consideration of the fate of women who have had repeated cesarean sections and what happens to those who had tubal ligation or salpingectomy.

In the course of preparing some of our figures for this report, we looked over the last 350 hysterectomies done for all reasons, to find out how many of those patients had had previous surgical procedures. In that particular group, 27 women had had either tubal ligation or salpingectomy, and 21 had had one or more previous cesarean sections.

The number of years which elapsed before ultimate hysterectomy was necessary in these patients varied but they finally required hysterectomy. It seems to me that it is false conservatism to elect to do salpingectomy or tubal ligation in a woman who has repeated scars in the uterus, and if, as Dr. Greene has stated, we consider sterilization necessary, then we believe that she should be prepared by discussing the problem thoroughly with her in advance, and doing total hysterectomy at that time.

DR. DYER (Closing).—This paper was made up of material collected from a private source (10 cases) and the Charity Hospital source of 75 cases.

Of the 75 cases, actually, 65 of them were in New Orleans and 10 were at one of our hospitals out of town, so you cannot figure an exact percentage of total hysterectomies in relationship to the total section rate shown.

We are doing about 150 sections a year in New Orleans alone. Of that group, those women who have had total hysterectomy would run somewhere between 10 and 12 per cent. As to delivery from below following cesarean section, we have had a number of those cases. We have not added them up, actually, because they are of minor interest.

You will remember Dr. Cosgrove's paper of a year or so ago, in which he reported a great number of women whom he had delivered from below following cesarean section. Our present philosophy is that, if the patient has had previous babies from below without any difficulty, and she is sectioned for other than pelvic contracture—as a rule, without an oversized baby—and if she comes in with the cervix completely dilated, and the head on the perineum, she is delivered from below.

I always feel that the residents on the service have coronaries that are a little better than mine. If they elect to sit at the side of the patient with 1,000 c.c. of blood and watch every movement she makes in labor, then, if progress is normal and they wish to deliver from below, it is perfectly all right, in the control group.

The "section saturation point" is just a phrase we coined. I think in your own minds you certainly know it is hard to describe.

Incidentally, Dr. Galloway, we do not do cesarean section hysterectomy for tuberculosis per se. If we did down there, we would have a tremendous rate. The patient who was mentioned in this group had had active tuberculosis, following which a thoracoplasty was done. It was a complete hysterectomy following cesarean section for the second time. She was a private patient.

The transverse incision, in our experience, causes less bleeding; we try to do it routinely. With this particular procedure the uterus is one-half amputated by the time the baby is delivered.

I am in complete agreement with Dr. Hamilton, and I think his phrasing of his feelings in regard to getting out in the open and calling it sterilization is certainly well taken.

I am sure there were no recorded injuries to ureter, bladder, or bowel with any of these procedures.

I skipped over one thing rapidly in trying to get this into the time limit. There is one sentence that states that oophorectomy is done only if there is some disease element as far as the ovaries are concerned, regardless of the patient's age.

NINETEEN-YEAR SURVEY OF MATERNAL MORTALITY AT THE COOK COUNTY HOSPITAL*

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(From the Department of Obstetrics, Cook County Hospital, and the Department of Obstetrics and Gynecology, Northwestern University Medical School)

THIS report concerns the maternal mortality in the obstetrical wards of the Cook County Hospital for the past nineteen years. These wards occupy a peculiar position in the large free hospitals of the United States. To them is sent every pregnant woman regardless of what pathologic condition is present. Thus, we are responsible for pregnant women with gunshot wounds of the abdomen, gastrointestinal carcinoma, acute leukemia, brain tumor, and many other conditions entirely unrelated to pregnancy. All patients in this series whose deaths were due to pregnancy per se have been so designated by the Subcommittee on Maternal Mortality of the City of Chicago.

Everyone knows the story of maternal mortality in the United States for the past twenty-five years. No one is quite able to explain completely the marked decrease in death due to pregnancy. For this reason, we thought a review of our fatalities over a period of years might be of interest.

During the period studied we had 104,123 live births in the hospital. Approximately one-fifth of the mothers had prenatal care in the hospital clinic. Three-fifths had prenatal care by outside agencies without hospital facilities or were referred by private doctors. One-fifth had no prenatal care.

Fig. 1 gives a general picture of all deaths which occurred in the wards for the nineteen-year period. Total number of deaths is indicated by the figures on the left, total number of live births by the figures on the right. The top line of the graph shows the total number of ward deaths. This includes a number of patients who were not pregnant, but were sent to the wards with diagnoses of pregnancy with associated pathology. The next line shows the yearly number of deaths in pregnant women. The third line shows the mortality in patients whose deaths were due to pregnancy. The last line shows the maternal deaths due to pregnancy less those due to abortion. This last line, we believe, requires some explanation. We have no idea that deaths from abortion are not obstetrical deaths. Nevertheless, we believe that our admission rate for abortions is far above that of the average hospital. This is particularly true when one remembers that most aborting patients enter the Cook County Hospital bleeding dangerously or infected to the point of incapacitation. The patients whom we serve seldom seek hospitalization without more than sufficient reason.

If we study the causes of mortality in more detail, we find the following facts:

Infection (Fig. 2).—

Infection always has been one of the three leading causes of maternal mortality, and until recently accounted for more deaths than any other single cause.

*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

In the last twenty years marked decrease of maternal death due to sepsis has been noted all over the nation, in fact, all over the world. Blood banks with blood readily available and in quantity have been invaluable. Our bank was started in March, 1937. We had some sulfanilamide, beginning in 1938, and penicillin was available to the wards in 1945 in limited amounts.

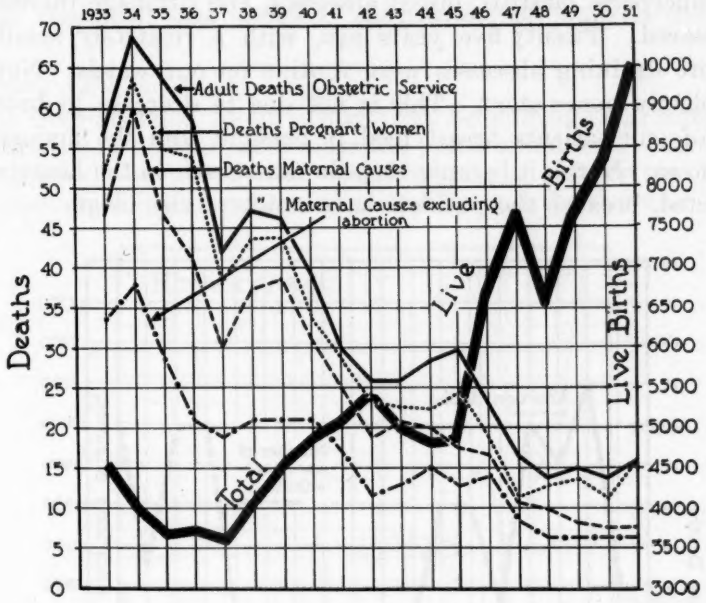
1933 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51
Deaths
Live Births
Adult Deaths Obstetric Service
Deaths Pregnant Women
Deaths Maternal Causes
" Maternal Causes excluding abortion
Births
Live
Total

Fig. 1.

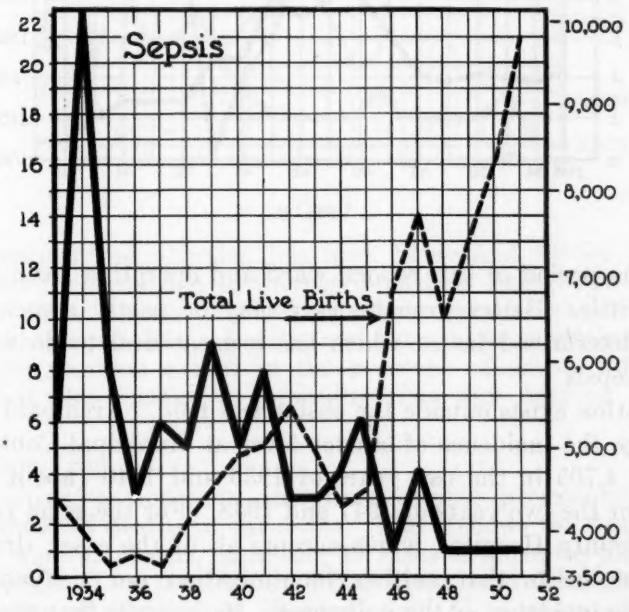

Fig. 2.

Nevertheless, we believe that there is an X factor which may be as important as blood banks or sulfonamides or antibiotics in the decreased mortality due to sepsis. Fulminating, fatal postpartum peritonitis following completely

normal delivery after easy normal labors was an all-too-frequent occurrence in our wards twenty-five years ago. It is so rare now that very few residents see a single case during their training period. This is not because the disease is controlled by modern methods. The disease does not occur.

Severe puerperal mastitis, breast abscesses, and drainage thereof have likewise disappeared. Twenty-five years ago, with a relatively small service, a dozen or more draining abscesses were routine on our wards. Now, they are almost completely nonexistent. This is not due to decrease in breast feeding, because all of our patients breast feed if possible, and the majority of them are able to do so. Nor is it because they do not return to the hospital if breasts become infected, because the patients have nowhere else to go.

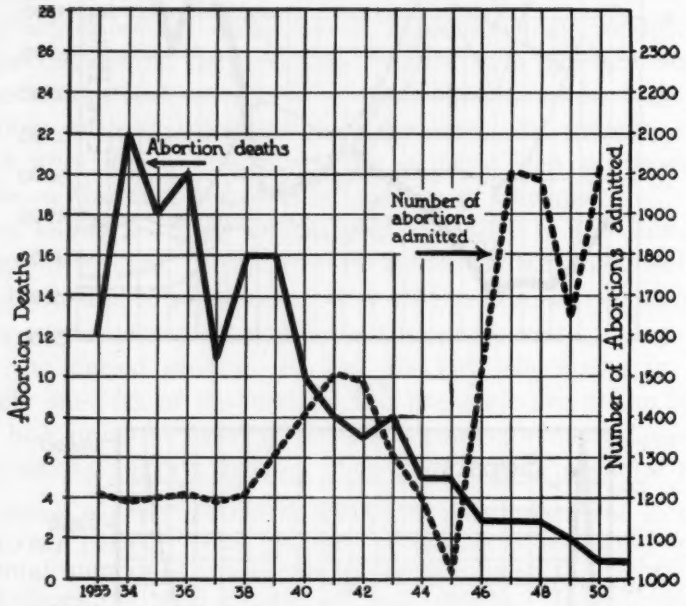

Fig. 3.

During the period of this report, ward and operating room techniques have changed but little. Better prenatal care may be partly responsible, but there is still an undetermined factor which has a great deal to do with the absence of puerperal sepsis.

This situation exists outside the obstetrical field. Archibald Hoyne[1] reports that in Chicago the incidence of scarlet fever at Municipal Contagious Hospital dropped from 4,705 in the two years of 1939 and 1940 (about normal for the time) to 451 for the two years of 1947 and 1948. For the same years, erysipelas[2] at the Cook County Hospital, which accepts all of the cases, dropped from 343 to 96. Hoyne insists that neither immunization nor sulfonamides had any influence on the incidence of these diseases. He believes that the decline in such infections is attributable to increased resistance by the patient, diminished virulence of the streptococci, and advances in sanitation.

Perhaps this X factor explains the safety of the extraperitoneal cesarean section, or the fact that in our wards we do ordinary transperitoneal sections

on patients in such condition that twenty years ago the operation would have been considered foolhardy, if not criminal.

At any rate, mortality from puerperal sepsis is rapidly reaching the vanishing point in our wards. Practically every death from sepsis we have had in recent years occurred in patients who came to the hospital with such advanced lesions that treatment was useless. They were not patients delivered in the wards.

Abortions (Fig. 3).—

Deaths from abortion result mostly from hemorrhage and sepsis. Although the sharp decline in deaths due to abortion began about 1937, the most dramatic changes happened about 1945-1946 when, in spite of a sharp rise in admissions, the total number of deaths decreased markedly and the decrease persists.

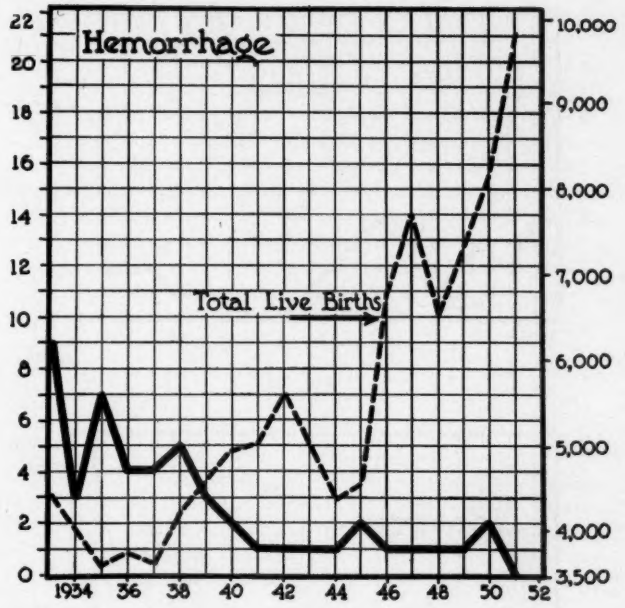

Fig. 4.

Active treatment of abortion has been liberalized in the past few years[3] because of need for beds due to increased patient load. For many years we did not curette patients until they had been temperature free for five days, unless hemorrhage threatened life. Lately we have been curetting every patient with incomplete abortion except in the presence of active infection. We do not believe that this change in procedure has any bearing on the lowered mortality.

Hemorrhage (Fig. 4).—

Next to sepsis, hemorrhage, including ectopic pregnancy, accounted for the largest number of deaths in our series. Fig. 4 shows the deaths from hemorrhage. There were 49 deaths, including 19 cases of abruptio placentae, 11 cases of ruptured uterus, 7 of postpartum hemorrhage, and 5 of placenta previa.

Of this group of 49 patients, 29 were admitted to the ward in severe shock due to excessive hemorrhage. If the term is not acceptable, the fact remains that 60 per cent of the deaths occurred in patients who were in marked jeopardy when they entered the hospital. Twenty-four, approximately 50 per cent, lived less than eight hours after they entered the hospital. Twenty-seven died before the blood bank was established.

Ectopic Pregnancy (Fig. 5).—

Eight hundred three ectopic pregnancies were operated upon from the wards during the nineteen-year period. During the same period a large number were operated upon from the general surgery and from the gynecology

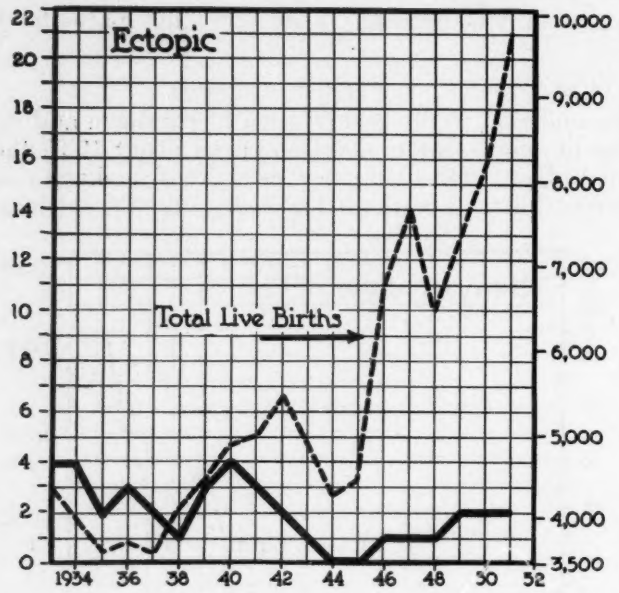

Fig. 5.

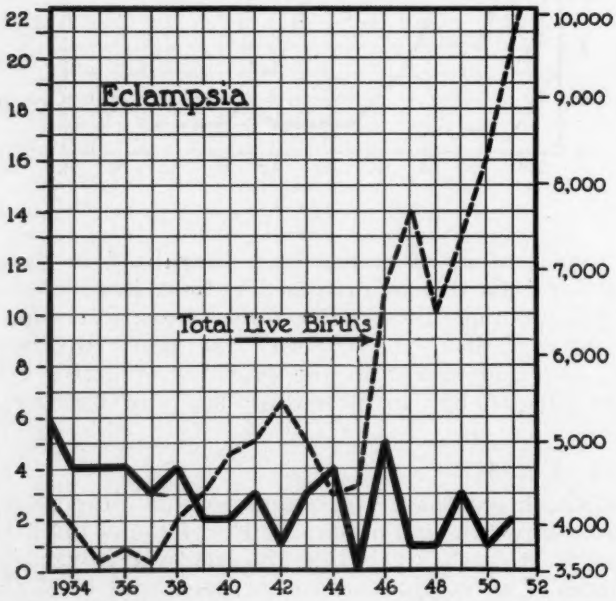

Fig. 6.

departments. These are not included in this report. The gross mortality was 4.73 per cent—one out of twenty, which is much too high, of course. Our series resulted in 38 deaths. Twenty-eight of these patients lived less than twelve

hours after hospitalization and of these, 11 died in 6 hours or less. This, we believe, is indicative of the condition in which patients are admitted to the wards. Death from ectopic pregnancy can be prevented only by: *early* hospitalization, *early* diagnosis, *early* blood replacement, *early* operation.

Patients admitted with irreversible changes due to hemorrhage will be little helped by blood replacement or control of hemorrhage.

Toxemia (Fig. 6).—

Deaths from toxemia diminish as prenatal care increases. Nevertheless, toxemia accounts for a high percentage of maternal deaths. In our series there were 415 patients with eclampsia. Fifty-three of these died. The gross mortality, therefore, is 13 per cent. It is evident that deaths from eclampsia can be prevented only by preventing eclampsia itself. In our 53 fatal cases, 29 patients had no prenatal care, 7 had completely inadequate care and were referred to the hospital at the time of their first visit to the clinic, and 3 refused hospitalization.

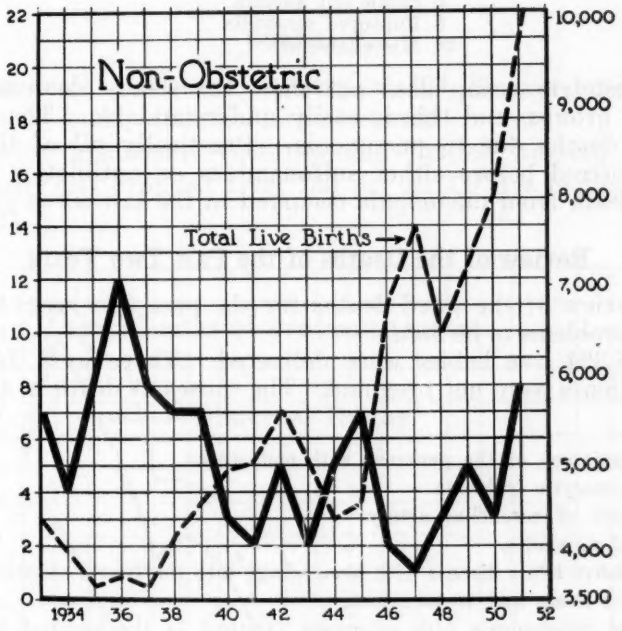

Fig. 7.

Twenty-eight of the 53, more than half, had convulsions before admission to the hospital. Fourteen died within twelve hours after hospitalization.

Included in the series there were 17 deaths from hypertensive disease not due to toxemia. These are only questionably maternal deaths. Ten of these women were pregnant six months or less and of these 4 not more than three months. Only 2 of the 17 had any prenatal care.

Organic Heart Disease.—

Gross organic heart lesions were present in 33 of all the patients who died. Twenty had no prenatal care. In only 22 of these cases was pregnancy considered the factor responsible for death. Of the 22 patients whose deaths were due to pregnancy, 9 had full-term deliveries, 5 delivered prematurely, 4 died undelivered (5 to 7 months), 3 died after hysterotomy, and 1 died 4 weeks post partum.

Other Obstetric Causes.—

There were 44 deaths in the series as a result of other obstetric causes which are listed as follows:

17 Pyelonephritis
13 Anesthesia
5 Hyperemesis gravidarum
4 Chorionepithelioma
3 Transfusion reaction
1 Acute yellow atrophy
1 Pituitrin reaction

Nonobstetric Causes (Fig. 7).—

Nonobstetric causes accounted for 97 of 590 deaths:

25 Pneumonia
20 Tuberculosis
11 Organic heart disease in which pregnancy was not a factor
8 Malignancy
8 Sickle-cell anemia
5 Ruptured appendix
20 Miscellaneous

The nonobstetric group does not show the steady decrease in mortality noted in other groups, and this is easily understandable. The great gain has been made in deaths due to pneumonia. Practically *all* of the deaths from pneumonia occurred before either sulfonamides or antibiotics were available, and only one death from pneumonia occurred in the last seven years.

Review of the Deaths of the Past Two Years

A short review of the ward deaths for the past two years will give a fair picture of the problems to be met.

In 1950, 8,394 live babies were delivered. There were 14 adult deaths. Of these, 2 patients were not pregnant. The causes of death in the 12 pregnant women were:

1. Adenocarcinoma of the pancreas with metastases.
2. Acute monocytic leukemia.
3. Thrombosis of cerebellar artery.
4. Ruptured appendix.
5. Hypertensive heart disease with hemorrhage into the fourth ventricle (patient in the hospital 4 hours and 10 minutes).
6. Advanced tuberculosis with eclampsia (patient in the hospital 30 minutes).
7. Sepsis after criminal abortion (patient in the hospital 2½ days).
8. Advanced puerperal sepsis. (Patient sent in 10 days after delivery, moribund. Unattended delivery with infanticide. Admission temperature 105.4° F.)
9. Lower nephron nephrosis following 3,500 c.c. transfusion for treatment of postpartum hemorrhage in abruptio placentae.
10. Ruptured uterus.
11. Massive pulmonary embolus in a patient who had been operated upon for ectopic pregnancy.
12. Intra-abdominal hemorrhage in a patient with undiagnosed ectopic pregnancy. This was a definitely preventable death.

In 1951 there were 10,121 live births. There were fifteen adult deaths. The causes of death included:

1. Diabetes with brain atrophy.
2. Miliary tuberculosis.
3. Status asthmaticus.

4. Frontal lobe abscess at 6 months' gestation.
5. Tuberculous meningitis.
6. Sepsis following criminal abortion.
7. Miliary tuberculosis with sickle-cell anemia.
8. Cerebral hemorrhage in a patient with chronic hypertension at 24 weeks' gestation.
9. Rheumatic heart disease (patient 30 weeks pregnant, not in labor).
10. Postpartum suicide.
11. Massive pontine hemorrhage in an eclamptic patient.
12. Ruptured ectopic pregnancy in a patient who died 20 minutes after reaching the ward.
13. Ruptured ectopic pregnancy three hours postoperatively.
14. Pulmonary embolus following repeat cesarean section.
15. Severe pre-eclampsia (death 24 hours after cesarean section; uric acid 25.2 mg. per cent).

No comment is made on these cases. They are detailed in order to show the large percentage of patients who arrive in the wards too late for helpful treatment.

Summary

1. Maternal deaths following delivery of 104,123 live babies in nineteen years at the Cook County Hospital are reviewed.

2. In spite of inadequate facilities and limited nursing personnel, the maternal mortality has dropped from 150 per 10,000 live births in 1934 to 7.9 in 1951 (Fig. 8).

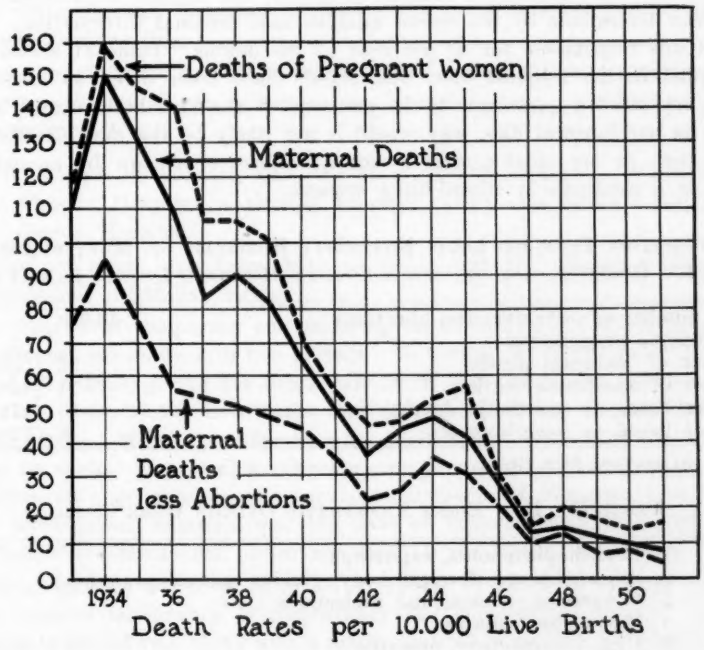

Fig. 8.

3. Reasons for the increased safety of motherhood are discussed. These include the sulfonamides, blood banks, the antibiotics, better prenatal care, increased awareness on the part of both physician and patient as to the necessity of prompt investigation of abnormal signs and symptoms.

4. The greatest hope for further lowering of maternal mortality lies in the complete elimination of deaths due to toxemia. Proper prenatal care, plus convincing physicians that mortality from toxemia is practically zero if convulsions are prevented, could accomplish this.

We wish to express our appreciation of the valuable assistance of Miss Sidonia Spinka, B.S., M.T., in the preparation of this article.

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Discussion

DR. LEO J. HARTNETT, St. Louis, Mo.—A study of this type represents considerable effort and application on the part of the essayists. The conclusions are sound from every standpoint, and while we are inclined to view the improvement in maternal death rate in this country at large much as a pleasant change in the weather, analysis brings out the tremendous effort in the accumulation and application of knowledge which was necessary. The authors have not mentioned that a great part in this improvement has been played by those teachers who have thoroughly trained their pupils during the past 19 years. I can take issue only with the last statment in their conclusions.

It is interesting to note that the authors have mentioned that out of 104,000 deliveries there were only 13 deaths from anesthesia, and the authors have informed me privately that 3 have occurred during the past five years. In the light of this information I am presenting Table I, analyzing the number of deaths in five of the better institutions in St. Louis during the past five years. This shows the number of births, the number of maternal deaths, and the cause, as was determined by the record analysis and personal information. You will see that anesthesia was responsible for 40 per cent of the deaths. Table II shows the cause of death as recorded in the hospital files, that should have been listed as anesthetic deaths. This brings to my mind a question: If 73 per cent of the anesthetic deaths are hidden in such a manner in our hospital files, why would it not likely be the case elsewhere? It must be understood that, in my opinion, this is not a deliberate attempt by anyone to mislead, but, rather, it is a weakness in record-filing systems.

Table I. Information From St. Louis Maternity Hospital, St. Mary's Hospital Group, St. Louis City Hospital, and St. Louis County Hospital During Last Five Years

Total number of deliveries (no abortions or ectopic pregnancies)	49,054
Number of maternal deaths	25 (0.05%)
Number of anesthetic deaths	11 (44%)
Number listed as anesthetic deaths	*3 (27%)
Number listed as something else	8 (73%)

*Two due to crossed feed lines.

Table II. How Eight Anesthetic Deaths Were Filed

1. Bronchopneumonia, aspiration
2. Aspiration of foreign body (under gas-oxygen-ether)
3. Congestion, edema, and atelectasis
4. Vasomotor collapse
5. Drug idiosyncrasy, procaine
6. Edema of larynx, due to poisoning (anesthetic)
7. Pulmonary edema, congestive heart failure
8. Pulmonary edema due to aspiration

We have antibiotics to combat and prevent sepsis, blood banks and better trained medical talent to combat hemorrhage and shock, prenatal care to combat the toxemias, but there is no protection against the improper application of anesthesia in the delivery room.

The exception, of course, is in those hospitals where the administration of anesthesia in the delivery room is under the supervision of competent anesthetists. I presume, therefore, that Cook County Hospital has such competent ones.

It has been my experience that obstetrical anesthesia has been avoided by the trained anesthetist, and tolerated, for the most part, by the obstetrician. It may be that the obstetrician has been trained somewhat in this field, and he feels confident that he can direct the administration under ordinary circumstances. The patient scheduled for the operating room is carefully prepared for anesthesia and the administration is exacting under the supervision of trained personnel. The obstetrical patient for the most part reaches the delivery table ill prepared for anesthesia, and with little thought as to its proper choice or administration. Such circumstances should require even more expert supervision than in the case of the operating room patient, and certainly should not be entrusted to the unskilled medical student, intern, or nurse.

What can be done to improve this troublesome situation? This can be done only when anesthetic deaths are assigned to the proper causes. Then, and only then, can we know how big the problem really is. We should have a better training program for the patient, wherein she can be taught to face parturition with less fear and apprehension in order that the benefits of local anesthesia and analgesia can be enhanced. Then if she remembers something about her delivery she will not think she has been mistreated. There will, of course, always be a certain percentage of unstable people. The department head must insist that the hospital administrator procure the necessary personnel trained in anesthesia. Many of the administrators apparently refuse to recognize the existence of this problem, in the hope that if they ignore it long enough it will go away.

It is apparent that training programs for obstetrical anesthesia for the most part are lagging. It is likewise obvious that a career as an obstetrical anesthetist or anesthesiologist is not highly desirable, and therefore hospital administrators must realize that there must be some compensation for this.

As the maternal death rate from other causes is reduced, the problem of anesthesia is likely to become the major one, unless we can recognize it as a problem and take effective measures to overcome it.

DR. C. R. MAYS, Shreveport, La.—We have recently reviewed our maternal mortality at Shreveport Charity Hospital, a general hospital caring for patients similar in type to those of Cook County Hospital.

The period of study was from 1941 to 1951, inclusive, during which time we had 28,915 admissions and 27,746 live births.

For the purpose of comparing our changing death rates and the distribution of causes of death, we divided our study into two periods. In period one (1941-1945) there were 9,164 live births and 36 deaths, giving the death rate of 39 per 10,000 live births. In period two (1946-1951) there were 18,600 live births and 27 deaths, giving a gross death rate of 14 per 10,000 live births. When these deaths were corrected to exclude abortions, ectopic pregnancies under 20 weeks' gestation, a miscellaneous group of medical diseases including two burns, one sickle-cell anemia crisis, one adenoma carcinoma of the colon, one nephrosclerosis, two cases of myelogenous leukemia and one case of typhoid fever, the corrected mortality was 28 per 10,000 live births for period one and 11 per 10,000 live births for period two.

The over-all picture of the distribution of causes of death in the two periods was one of increasing relative importance of hemorrhage and coincidental medical complications as a cause of death in period two, along with a nearly stationary position of toxemia of pregnancy as a lethal factor. There was a sharp drop in the frequency of deaths from sepsis in period two.

Forty-four per cent of the deaths from sepsis occurred among 4,185 patients admitted in 1941 and 1942. Among the last 21,328 admissions since 1944 we would have had only one genital-tract death from sepsis had we not experienced a foreign body accident at a hysterectomy for ruptured uterus.

It is of interest that the patients who died from hemorrhages in period one received an average of 1,520 c.c. of blood, while for those who died from hemorrhage in period two, the average volume of blood and plasma transfused before death was 4,370 c.c. Four of 13 deaths from hemorrhage in period two were from sequelae of shock in the form of lower nephron nephrosis, bilateral cortical necrosis, and pituitary necrosis.

In the second period of our analysis there has been a percentagewise rate of decrease of 62 per cent in over-all mortality, 57 per cent decrease in corrected mortality, a 34 per cent decrease in mortality from hemorrhage, an 89 per cent decrease in mortality from postpartum sepsis, a 63 per cent decrease in mortality from toxemia of pregnancy, and a 67 per cent decrease in mortality from accidents of pregnancy.

We delivered these patients, in period one, with a staff of one visiting man, one resident in training, and two interns. In period two we have had an adequate resident and visiting staff. These women were delivered from only forty-five beds. Next year we will move into a new physical facility with the romantic and very sectional title of "Confederate Memorial Hospital."

The organization of a good resident training program has yielded us a very gratifying, though not yet satisfying, maternal mortality rate.

DR. RUDOLPH W. HOLMES, Charlottesville, Virginia.—I have had an abiding interest in the work of the County Hospital since I was a member of the medical staff all of forty years and more ago. The County Hospital has held a unique position in the medical world ever since its origin nearly one hundred years ago, and that is peculiarly true of the obstetric service. "The County" was about the first hospital in Chicago to have a provision for confinements. To be comparable, figures must be reduced to a common denominator; every endeavor to contrast the activities and mortality rates of diverse hospitals is surely going to give invidious answers unless the background of the various units is fully appreciated.

Chicago almost from its origin was a cosmopolitan city; especially in its early years its population increments resulted from immigrations of peoples of the world. They brought with them their national tongues, their customs, their traditions, their habits of isolationism, so the city seemed to be sectioned off into alien communities; in their obstetric habits they quite commonly were all unified in that they employed midwives to the extent of fetishism. In the dawn of this century about 60 per cent of all confinements were in the hands of these women, largely untrained, ignorant, and inspired by vicious superstitions. (In a recent census report there were only 128 deliveries conducted by midwives.) The *midwife peril* became an acute agony in the late eighteen nineties; the hospitals had not awakened to the necessity of providing an obstetric service within their walls. To be sure, a certain few hospitals did provide a few beds for obstetrics but the facilities were so inadequate, so crude, that their value was negligible. It was essentially true that the County Hospital was the only institution which provided an isolated division for infected patients, a ward with some twenty or more beds, usually fully occupied. Parenthetically, a deputy coroner, and a deputy coroner's physician had definite quarters within the hospital, holding inquests on patients who died from violence (accidents, murders, suicides, criminal abortions, etc.).

The conditions of the times being what they were, The County had to receive the great mass of mismanaged, neglected, and abused patients afflicted with lethal complications for which midwives were responsible. If the quoted puerperal mortality rate were 2 per cent, it was not startlingly high considering the character of the flotsam brought to the hospital doors; rather, the fact that 98 per cent of the clientele recovered was an accolade to the staff. In late years the County Hospital has developed a highly efficient maternal welfare service which a large proportion of prospective inmates accept gratefully; nevertheless, a goodly proportion of the patients neglect to avail themselves of the service. I would stress the fact that the County must accept all comers; the County continues to receive mismanaged, neglected patients, seriously compromised. Neither the type of patients, nor the high incidence rates of complications are comparable to those of many maternity services where the class of patients is selected so that their patients rarely die. With these facts before you, you will appreciate that the data accumulated by Drs. Fitzgerald and Webster reveal efficient and successful maternity service.

INTRAEPITHELIAL CARCINOMA OF THE VULVA*

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CARCINOMA of the vulva probably exists in the intraepithelial phase more frequently than is generally reported. This is of considerable clinical importance because of the currently high mortality rate associated with vulvar carcinoma. The recognition of the preinvasive lesion followed by adequate surgical removal would contribute materially to an increased survival rate.

A review of the microscopic pathologic material of 112 cases of carcinoma of the vulva from the Indiana University Medical Center (63 cases) and the Indiana State Board of Health Tumor Registry (49 cases) from 1937 to 1952, revealed 2 cases in which the lesion was entirely intraepithelial and 6 cases of intraepithelial surface involvement associated with a varying extent of invasion.

This report is based on a study of these 8 cases which represent 7 per cent of the vulvar carcinomas.

Analysis of Cases

Past History.—There was no characteristic age incidence, the patients' ages ranging from 29 to 78 years. All patients were parous. None gave a history of previous skin disease, arsenical treatment, or x-ray therapy to the vulva.

Symptoms.—Each patient complained of vulvar itching and burning of the vulva on urination for periods varying from 2 to 24 months. At some time after the appearance of the pruritus each had noted a small lump on the vulva. Pain was not an outstanding symptom. Only one patient complained of a tumor which had a watery or bloody discharge.

Gross Appearance of Lesions.—Intraepithelial carcinoma usually appears as a reddened, velvety, flat or slightly elevated, well-delineated lesion of the vulva. There may be multiple small lesions. In the early lesion there is no crusting, weeping or bleeding. The invasive phase of the carcinoma manifests itself by the appearance of nodulation or ulceration in the center of the lesion. The surface epithelial involvement may gradually spread to include large areas of the vulva and may extend on to the vaginal mucous membrane.

Microscopic Findings.—The epithelium is usually of normal thickness, although in some cases there is some thinning and in others slight acanthosis. There is a diminution or absence of the keratin layer. Characteristically, there occurs a complete loss of the normal stratification or polarity of the epithelial cells with an absence of the usual progressive maturation from the basal cells outward. Under high power the cells appear highly undifferentiated. The epithelial cells and their nuclei vary considerably in size and shape, the

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latter showing increased depth of staining reaction. There are numerous mitotic figures throughout the thickness of the epithelium. These are out of proportion to any inflammatory reaction which may be present. Abnormal mitotic figures are found. Encountered, but not considered characteristic, are multinucleated giant cells, individual cell keratinization, balloon degeneration, and necrobiotic changes. Intercellular bridges are sometimes maintained although there is a general loss of cohesiveness. Plasma cells, lymphocytes, and evidences of increased vascularity are found in the corium. When invasion does occur the malignant cells usually maintain a high degree of undifferentiation in both the local invasion and the lymph node metastases.

Case Presentations

A. Cases With Prolonged Preinvasive Phase of Carcinoma of the Vulva.—The first two cases to be presented represent carcinoma of the vulva with a prolonged preinvasive phase, 7 and 11 years elapsing between the microscopic diagnosis of intraepithelial carcinoma and the appearance of the invasive phase.

CASE 1.—E. P., a 42-year-old housewife, was admitted to a local hospital in July, 1945. She complained of vulvar itching and several small vulvar sores of 1 year's duration. Examination showed small, reddened, flat, circumscribed lesions of both labia. A simple vulvectomy was performed. The microscopic examination revealed multiple areas of typical intraepithelial carcinoma (Fig. 1). Four years later, in March, 1949, she was admitted to the Indiana University Medical Center (No. 130511) by another physician, because of a recurrence of the vulvar lesions and a small exophytic lesion of the cervix uteri. The multiple vulvar lesions were biopsied and showed intraepithelial carcinoma with no invasion (Pathology No. 52180). Two of the larger vulvar lesions were treated by radium needle implantation. (Cervical biopsy revealed squamous-cell carcinoma, Grade I-II. The cervical lesion was classified as a Stage I and received x-ray radiation and radium.)

Her next admission was in July, 1951, because of recurrence of the vulvar lesions, several of them being 2 to 3 cm. in diameter. A complete vulvectomy was performed with removal of a generous border of normal skin and mucous membrane beyond the lesions. Microscopic examination of multiple sections showed only intraepithelial carcinoma with no evidence of invasion (Pathology No. 61648).

In August, 1952, she was again seen because of recurrent pruritus vulvae. Examination revealed multiple flat, red, velvety, well-circumscribed, 5 mm. sized lesions on the vulvar area. Further surgery was contemplated and was performed elsewhere. The multiple vulvar lesions were excised in September, 1952, and on microscopic examination in one area definite evidence of invasion was discovered. A diagnosis of Grade II invasive carcinoma was made (Fig. 2).

Thus, this squamous-cell carcinoma of the vulva had persisted in an intraepithelial, preinvasive phase for a period of 7 years after its microscopic diagnosis and 8 years from the time of appearance of the original symptoms, before it progressed into an invasive phase.

The cervical carcinoma responded well to the x-ray and radium and at none of the subsequent examinations has there been any evidence of recurrence.

CASE 2.—D. H., Indiana University Medical Center No. 31003, at the age of 67 years was admitted to the Indiana University Medical Center in June, 1940, by her private physician because of a 5 mm. sized reddened, slightly raised, well-circumscribed lesion on the upper right labium minus. This lesion was excised and revealed intraepithelial squamous-cell carcinoma of the vulva with no evidence of invasion (Pathology No. 39944) (Fig. 3). On the same admission a biopsy of a cervical lesion showed squamous-cell carcinoma, Stage I, which was treated by x-ray radiation and radium.

Eleven years later, in December, 1951, she was admitted to another local hospital by her private physician because of vulvar itching and the recurrence of a movable, reddened,

Fig. 1.

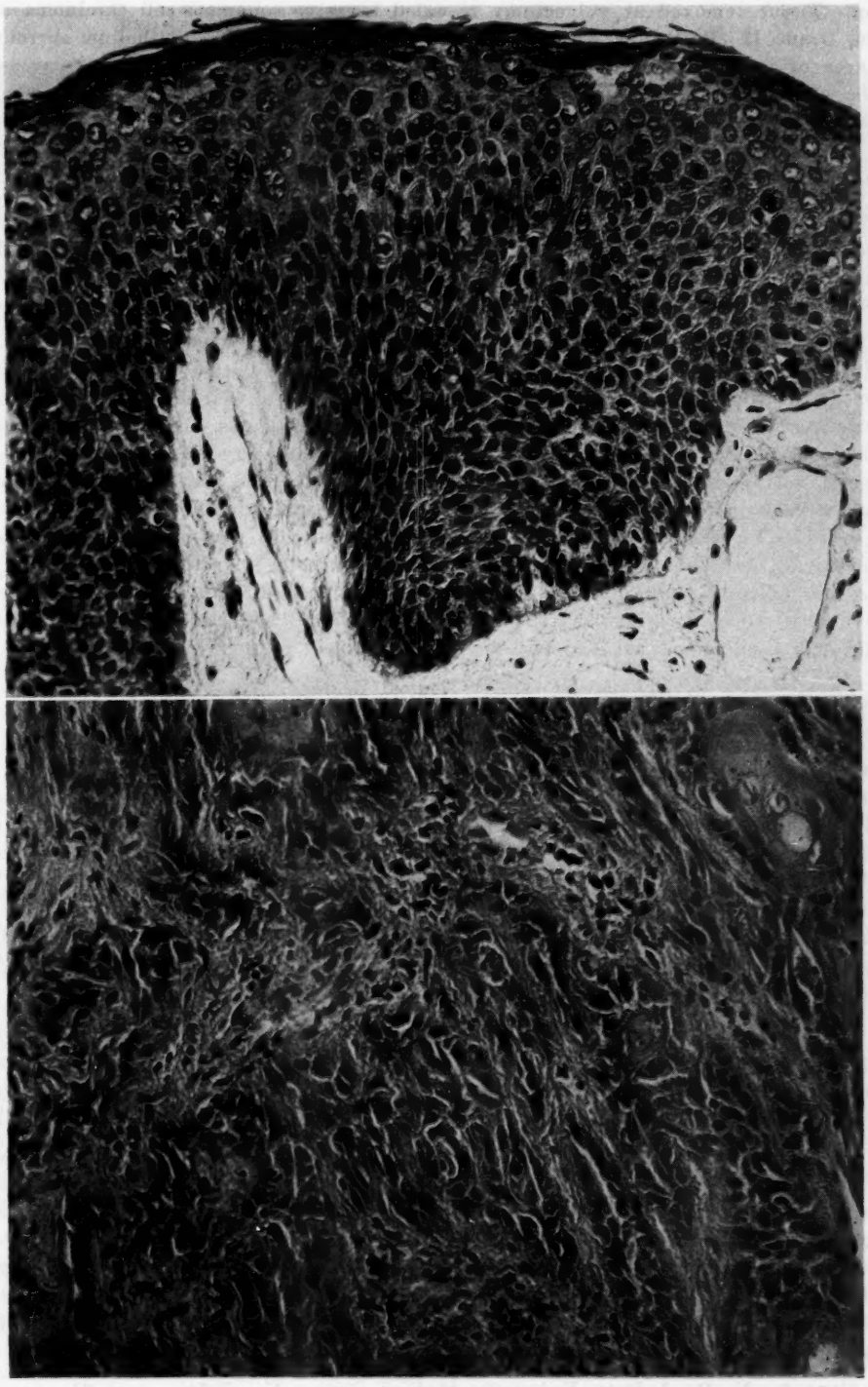

Fig. 2.

Fig. 1 (Case 1).—Vulvar tissue removed in 1945. Carcinoma exclusively in the intraepithelial phase.

Fig. 2 (Case 1).—Vulvar biopsy taken in 1952, seven years later, showing invasive carcinoma.

7 mm. sized lesion on the right labium minus at the site of the previously removed labial lesion. Tissue removed at vulvectomy revealed invasive squamous-cell carcinoma of the vulva, Grade II (Pathology No. S-51-5706) (Figs. 4 and 5). The epithelium surrounding the area of invasion showed the same intraepithelial carcinomatous involvement as seen in the original tissue 11 years previously. Pelvic examination revealed no evidence of recurrence of the cervical carcinoma.

In this case apparently the intraepithelial phase of the vulvar carcinoma had persisted for a period of 11 years prior to its progression into the invasive phase.

B. Cases With Extensive Preinvasive Surface Involvement Associated With Invasion.—In the next two cases the lesions were grossly characteristic of the preinvasive phase of carcinoma of the vulva, but upon microscopic examination invasion was demonstrated.

CASE 3.—R. L., Indiana University Medical Center No. 65905, aged 62 years, was admitted March 14, 1951, eight years following successful radiation therapy for a Stage I carcinoma of the cervix uteri. An examination revealed a well-delineated, red, velvety, slightly raised lesion 3 by 4 cm. in size, on the right labium minus. Biopsy from the margin of the vulvar lesion showed intraepithelial carcinoma (Pathology No. 60557) (Fig. 6). A complete vulvectomy was performed and multiple blocks and sections of the tissue revealed invasive carcinoma, Grade IV, surrounded by intraepithelial carcinoma (Pathology No. 60631) (Fig. 7). A bilateral inguinal node resection was performed and showed metastatic carcinoma in the deep inguinal nodes (Pathology No. 60839). In May, 1952, biopsy of multiple small, red, well-circumscribed lesions adjacent to the urethral orifice showed recurrence of carcinoma (Pathology No. 62327). These did not respond to radium radiation, and additional surgical excision was performed.

CASE 4.—P. T., Indiana University Medical Center No. 171415, aged 68 years, was admitted July 15, 1952, because of pruritus vulvae of 1 year's duration. She was a diabetic patient with gangrene of the right great toe. Examination revealed a well-circumscribed, 4 by 4 cm. lesion of the right labium majus. The area was reddened, soft, slightly elevated, without evidence of bleeding, exudate, or necrosis. The lesion was freely movable, with slight induration of the central portion. Because it was grossly characteristic of intraepithelial carcinoma, the lesion was completely removed for microscopic examination prior to a final decision as to ultimate therapy. Microscopically, the lesion was a circumscribed intraepithelial carcinoma with a definite border between it and normal epithelium with a small area of early invasion in the central portion, Grade III-IV (Pathology No. 65760). On the basis of these findings a complete vulvectomy was performed. Multiple sections failed to demonstrate additional carcinoma.

C. Cases With Clinically Invasive Carcinoma With Peripheral Intraepithelial Changes.—In the next four cases the lesions were grossly characteristic of the invasive phase of carcinoma of the vulva. Microscopic examination revealed intraepithelial carcinoma at the periphery of the invasive neoplasm.

CASE 5.—M. H., Indiana University Medical Center No. 7044, aged 63 years, was admitted in May, 1935, because of itching and burning associated with a small papillomatous lesion of the right labium majus. This was excised and microscopic examination revealed a low-grade, invasive carcinoma (Pathology No. 13514). Incomplete vulvectomy was performed 2 years later because of local recurrence (Pathology No. 18300). Complete vulvectomy was finally performed in November, 1939 (Pathology No. 23284). Microscopic examination of both vulvectomy specimens revealed invasive carcinoma, Grade III-IV, with a border of inrtaepithelial carcinoma. No follow-up information is available.

CASE 6.—N. P., Indiana University Medical Center No. 79760, aged 61 years, was admitted in June, 1944, with a complaint of itching of the vulva for 2 months. Examination revealed the entire area of the fourchette to be replaced with a fungating, firm, necrotic lesion involving the posterior one-third of both labia and extending into the posterior vaginal wall. Superficial inguinal lymph nodes were palpable bilaterally. A

Fig. 3.

Fig. 4.

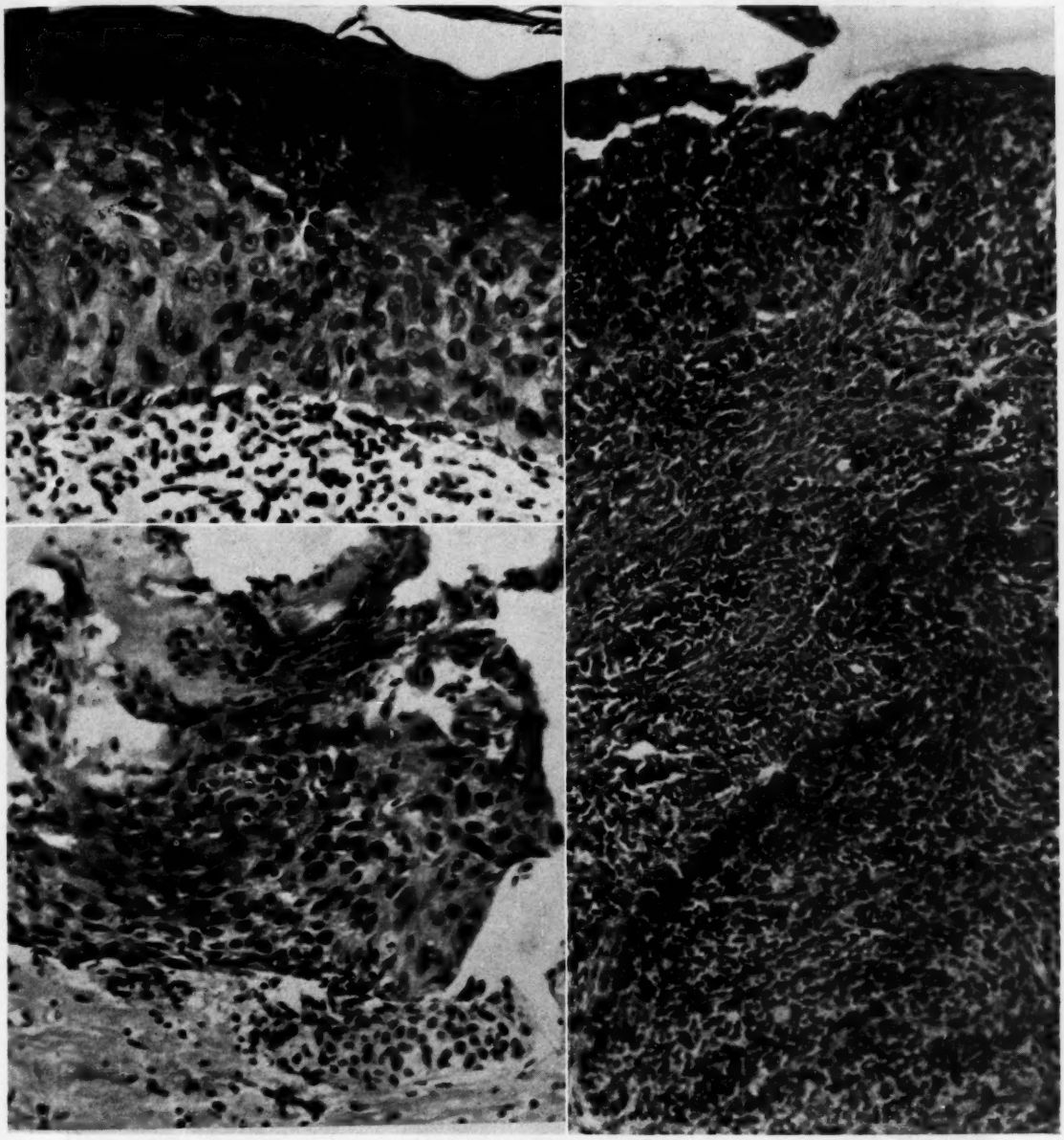

Fig. 5.

Fig. 3 (Case 2).—Vulvar tissue removed in 1940. Carcinoma exclusively in the intraepithelial phase.

Fig. 4. (Case 2).—Vulvar tissue removed in 1951, eleven years later, showing invasive carcinoma.

Fig. 5 (Case 2).—Surface epithelium of vulvar tissue removed in 1951 showing persistence of intraepithelial carcinomatous change.

Fig. 6.

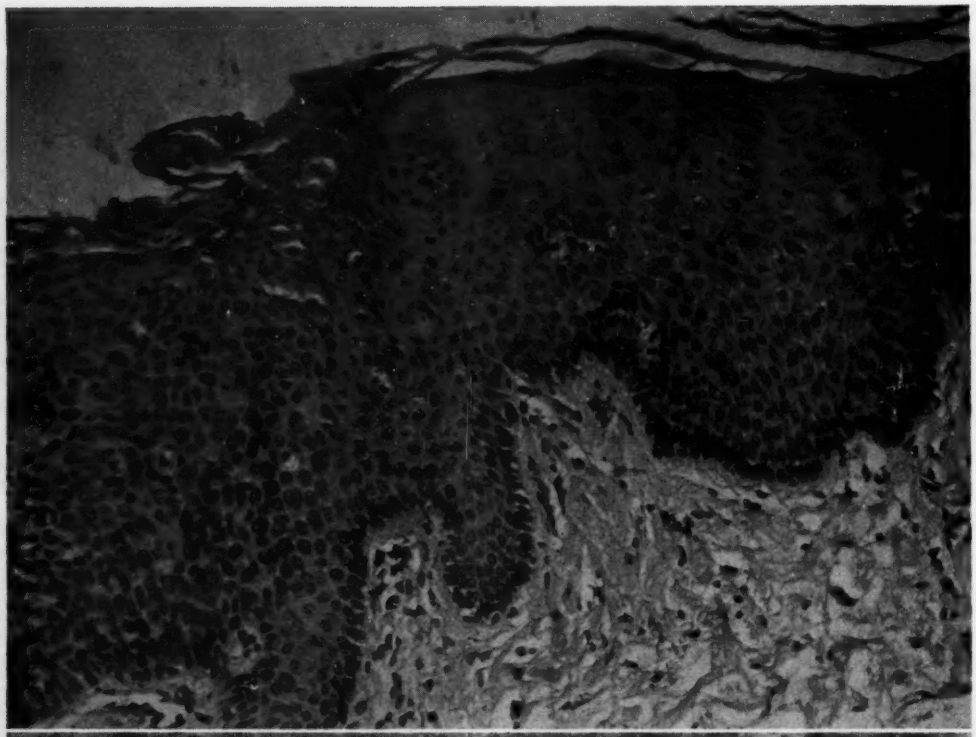

Fig. 7.

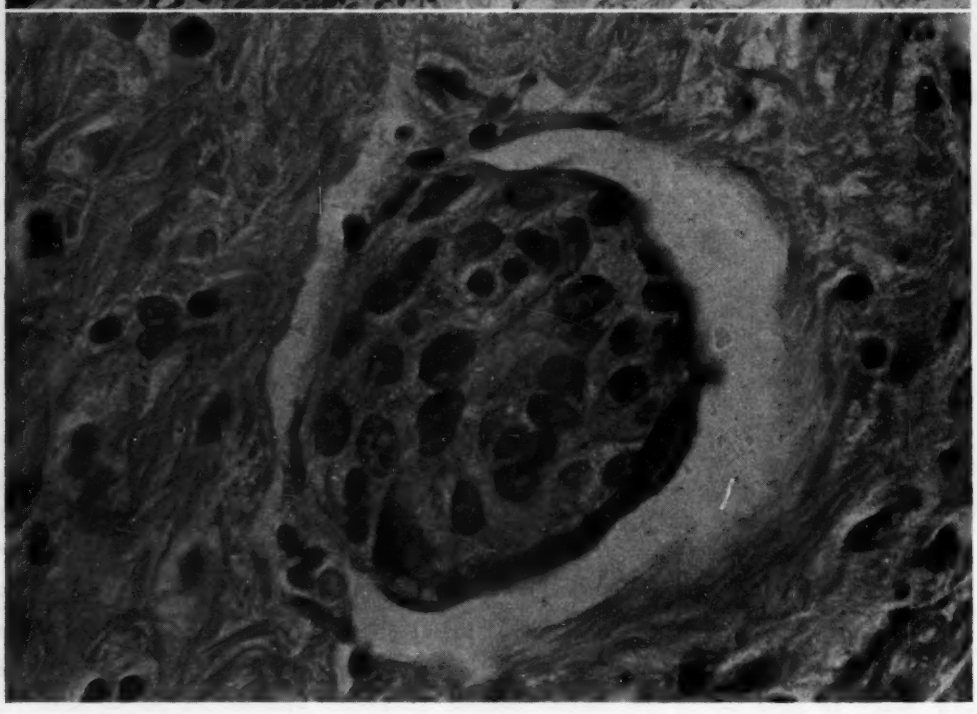

Fig. 6 (Case 3).—Vulvar biopsy showing junction of the intraepithelial carcinoma and the normal epithelium.

Fig. 7 (Case 3).—Vulvectomy tissue showing lymph channel filled with carcinoma.

complete vulvectomy was performed followed by radiation of the inguinal areas. A recurrence of the vulvar lesion was treated with radium needle implantation in January, 1945, and this was followed by bilateral inguinal node resection. There was metastatic carcinoma involving the deep and superficial nodes bilaterally (Pathology No. 38747). The patient was living and well and apparently free of disease in July, 1952. Microscopic examination of the original vulvectomy specimen (Pathology No. 37418) and of the biopsy of the recurrent lesion (Pathology No. 38219) revealed intraepithelial carcinoma bordering the extensive invasive lesion, Grade III-IV.

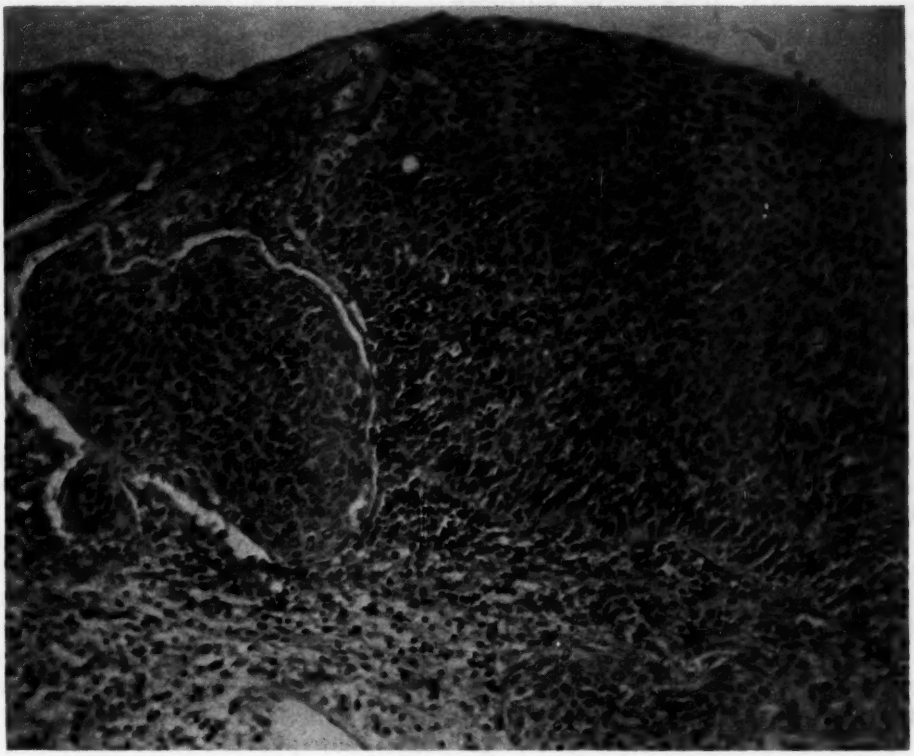

Fig. 8 (Case 6).—Vulvectomy tissue showing intraepithelial carcinomatous changes bordering on an area of invasive carcinoma.

CASE 7.—C. H., Tumor Registry No. 105, aged 61 years, was admitted to another hospital in October, 1948, for removal of an ulcer of the right labium minus. This was 5 mm. in diameter and, following partial vulvectomy, slides were forwarded to the Tumor Registry for microscopic study. These showed intraepithelial carcinoma bordering an area of Grade III-IV invasive neoplasm. Complete vulvectomy was subsequently performed and the patient is at present living and well.

CASE 8.—E. M., Tumor Registry No. 549, aged 29 years, was admitted to another hospital in December, 1948, for removal of a 9 by 6 mm. ulcerated lesion on the right labium majus. Excision of the right labium was performed and tissue forwarded to the Tumor Registry. This revealed an intraepithelial carcinoma bordering a Grade III-IV invasive carcinoma. At present she is living and well.

Nature of the Vulvar Epithelium Adjacent to Invasive Carcinoma

It was assumed that a study of the area adjacent to invasive neoplasm might give some information concerning the nature of the epithelium from

which invasive carcinoma develops. A careful review of the microscopic slides of the 112 cases of carcinoma of the vulva shows that the epithelium adjacent to the area of invasion can be classified into a number of categories (Table I).

TABLE I. VULVAR EPITHELIUM ADJACENT TO INVASIVE CARCINOMA

Normal epithelium	44%
Leukoplakia	23%
No bordering epithelium	22%
Intraepithelial carcinoma	7%
Kraurosis	4%

The majority of these observations were based upon the examination of a limited number of slides from each case. Gross specimens were not available for further study. Unfortunately, biopsies were frequently taken from the central portion of the gross vulvar lesion and the surgical specimens were not sectioned to include surrounding epithelium.

Taussig[1] believed that leukoplakia of the vulva played a predominant role in the development of vulvar carcinoma. Recent studies by Langley, Hertig, and Smith[2] showed only one patient in 122 with surgically treated leukoplakia of the vulva developed carcinoma during a five-year or longer follow-up, although 72 patients showed recurrence of symptoms or lesions or both. Miller[3] and his group found leukoplakic vulvitis associated with carcinoma of the vulva in 23 per cent of the cases.

In considering the occurrence of intraepithelial carcinoma and its relationship to invasive carcinoma, it is important to recognize that inflammatory acanthosis can produce a microscopic picture which closely resembles both leukoplakia and the intraepithelial lesion. This may be the background for the variation in statistics previously presented. In the original review of our material, sections from approximately 30 cases were considered as showing possible intraepithelial changes. Further study led to the interpretation of all but 8 as inflammatory acanthosis or leukoplakia.*

An additional 32 cases of leukoplakic vulvitis and 22 cases of chronic vulvitis from our own laboratory were reviewed, and no instance of intraepithelial or invasive carcinoma was found.

Table II correlates the Broder's grading of the invasive carcinoma with the nature of the epithelium adjacent to the invasive area. It is seen that the lower grades of malignancy are found most consistently in neoplasms developing in leukoplakia or normal epithelium.

Invasive carcinoma arising in intraepithelial lesions showed a high grade of malignancy in those cases in which the preinvasive phase was short, but in the 2 cases with a long intraepithelial phase, a well-differentiated carcinoma was encountered.

TABLE II. BRODER'S GRADING OF CARCINOMA OF THE VULVA CORRELATED WITH TYPE OF EPITHELIUM ADJACENT TO INVASION

	GRADE I	GRADE II	GRADE III-IV	
Normal	1	40	7	48
Leukoplakia	1	24	1	26
No bordering epithelium	0	22	4	26
Intraepithelial carcinoma	0	2	6	8
Kraurosis	0	3	1	4
Total				112

*This opinion has been concurred in by Dr. Zola Cooper, who was kind enough to review the material with us.

Differential Diagnosis

Intraepithelial carcinoma of the vulva is to be differentiated from Paget's disease, Bowen's disease, arsenical dermatitis, radiation dermatitis, inflammatory acanthosis, and leukoplakia.

Paget's disease is an eczematoid ulcerated lesion characterized by tingling, pain, and itching. Microscopically, the characteristic large clear ovoid or round Paget cells, devoid of prickles, are scattered throughout the epidermis.[4]

The term Bowen's disease should not be used synonomously with intraepithelial carcinoma, but should be limited to the lesion described by Bowen[5] as "a chronic affection of the skin which may attack any portion of the integument and begins as a papule, pale red, or the color of normal skin. This papule is covered by a thick layer which may be excessive and usually is combined with serous exudation to form a cornified crust. These papules increase to form lenticular or rounded, nodular lesions which may remain discrete or often tend to be grouped or confluent. When the crust is removed, the surface beneath is found to be red and oozing, granular, and sometimes slightly papillomatous in appearance." The corps ronds and monster cells with multiple nuclei clumped together characteristic of Bowen's disease are not found in intraepithelial carcinoma.

Arsenical dermatitis and radiation dermatitis are differentiated on the basis of the history.

Inflammatory acanthosis is most frequently found on the border of an ulcerative vulvar neoplasm and is characterized by the thickening of the epithelium, downgrowth of the rete pegs, increased number of normal mitotic figures, and diffuse infiltration of inflammatory cells. There is normal stratification.

Leukoplakia is characterized by an absolute increase in the thickness of the epithelium with hyperkeratosis and parakeratosis, acanthosis with or without mitotic figures, and a thickening of the rete pegs with downward extension. The corium usually shows degenerative changes in collagen and elastic tissue with acute or chronic inflammatory infiltration.

Comment

Microscopic demonstration of an intraepithelial carcinoma of the vulva may indicate one of three possibilities:

1. The existence of a lesion exclusively in the intraepithelial phase which is destined to become an invasive lesion (Cases 1 and 2).
2. The existence of invasion elsewhere even though the tissue removed for pathological study may show only the intraepithelial phase (Cases 3 and 4).
3. The tissue has been removed from the border of an invasive lesion (Cases 5, 6, 7, and 8).

The failure to find microscopic evidence of intraepithelial carcinoma indicates either that insufficient tissue has been removed at the border of an invasive lesion or that the intraepithelial phase has been completely destroyed by the growth of invasive carcinoma.

It is to be hoped that adequate biopsy of all suspicious vulvar lesions will demonstrate the existence of the intraepithelial phase more frequently and that more complete study of surgically removed vulvar lesions will substantiate the observation that the intraepithelial phase exists at the border of invasive lesions.

It is believed that the demonstration of an intraepithelial carcinoma of the vulva is indication for complete vulvectomy. If the invasive phase is

demonstrated, radical inguinal node resection should be performed. Inguinal node resection is not necessary if, after careful multiple block microscopic study, the entire lesion is an exclusively intraepithelial carcinoma.

The high incidence of cervical carcinoma in these cases of carcinoma of the vulva is considered an indication of a biologic sensitivity to neoplasm formation in the individual patients. Careful microscopic study failed to reveal any evidence of metastatic origin of the vulvar lesions.

Summary

One hundred twelve cases of carcinoma of the vulva have been reviewed. In two cases the intraepithelial phase persisted for seven and eleven years, respectively, before the invasion occurred. In two cases there were large intraepithelial lesions with early central invasion. Four cases were grossly characteristic of invasive carcinoma with microscopic evidence of intraepithelial carcinoma at the periphery of the invasive neoplasm.

It is reasonable to assume that invasive carcinoma of the vulva is preceded by an intraepithelial phase which may be of long or short duration, and which is recognizable by careful clinical and microscopic study.

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Discussion

DR. A. N. ARNESON, St. Louis, Mo.—Preinvasive cancer is to be found in a number of different structures in the body. The focal point of principal interest has been in the cervix. One might expect a similar natural history to apply to all intraepithelial lesions. In the case of genital epithelia, that possibility should be increased by virtue of a common physiologic and anatomic relationship.

The first two cases described by the authors present evidence of slow transition to invasive cancer, which has been documented many times in cervical lesions. Their cases revealing invasion only after microscopic examination of the surgically removed specimen have similar counterparts in the cervix, as do their clinically evident vulvar cancers with marginal regions showing intraepithelial cancer. Of special interest, however, is the fact that 3 of the 8 patients with vulvar cancer are found to have, at some time during observation, an associated carcinoma of the cervix. In a very cursory review of intraepithelial cancer of the vulva at the Barnard Free Skin and Cancer Hospital we found four patients admitted there since 1949. One of those had been treated two years earlier for invasive cancer of the cervix.

In pursuit of the association between vulvar and cervical cancer, the vulvar cases admitted to the Barnes Hospital from 1950 were reviewed. A total of 12 invasive lesions were found, but none associated with cervical cancer. The 4 intraepithelial cases at the Barnard Hospital were taken from a total of about 40 invasive cases admitted during the period in question. The one associated with cervical cancer presents an incidence of approximately 3 per cent. The data are admittedly inadequate, but it appears that further investigation is indicated. In all probability the relation of intraepithelial vulvar cancer to carcinoma of the cervix is a factor of coincidence.

Among the 4 intraepithelial vulvar lesions at the Barnard Hospital, one patient presented spread over the right side that involved both labia, the clitoris, and the labium minus on the left. There was, in addiiton, a discrete lesion on the left that was also pre-

invasive. Vulvectomy with superficial node dissection was done without finding evidence of lymphatic dispersion. Node dissection was performed in one other patient without evidence of involvement. There is no reason to assume lymph node dispersion in a true case of preinvasive cancer. Proof of intraepithelial status, however, is almost as difficult for vulvar as for cervical lesions. At the same time one must guard against too limited local excision of the primary lesion. Preinvasive cancer of the cervix may involve all or part of the vagina. We have one patient in whom the lesion overlaid the endometrium and extended into the tubes. Invasive cancer of the vulva may spread into the vagina, and that pathway could be available for intraepithelial lesions.

Preinvasive cancer of the vulva may be more frequent than is generally recognized. The tendency toward thin, superficial, invasive growth spread over a considerable area is more common for the vulva than for the cervix. The clinical description given by the authors for intraepithelial forms applies equally well to certain invading cancers. We are indebted to the authors for their investigation upon this subject, and for their attempts to explore factors contributing to etiology. The immediate stimulus responsible for malignant growth is vague, but resistance of the host's tissues must be a determining factor in natural history and in the gross form assumed by the growth.

DR. LAMAN A. GRAY, Louisville, Ky.—The present description of carcinoma in situ is particularly interesting because of the extraordinarily good colored microscopic slides demonstrating the changes in the basal epithelium and the nuclear abnormalities.

Five years ago we first observed a woman of 38 years with a small reddened edematous lesion with slight excoriations on the upper inner surface of the right labium majus, present for two weeks. Six weeks later this lesion, which was quite localized and 1.5 cm. in diameter, had developed a thick white appearance typical of localized leukoplakia. The remainder of the vulva was entirely normal, the vagina showed a full estrogenic effect, and menstruation was normal. Local excision of this lesion showed carcinoma in situ with complete change in the entire increased thickness of the epithelium to carcinoma-like cells but with no demonstrative invasion in numerous blocks. This patient then had a simple vulvectomy, followed by no recurrence with five years' observation.

While localized or characteristic leukoplakic lesions involving the inner surfaces of the labia majora and minora may occur before the menopause, they are far more common following the menopause. Within leukoplakia there may develop changes typical of carcinoma in situ, as described many years ago by Hinselmann. It would seem that we are calling an old lesion, leukoplakia Grade III, by a new name, carcinoma in situ. However, this is important in order to draw attention to and to diagnose further early, premalignant lesions of the vulva.

DR. CHARLES E. GALLOWAY, Evanston, Ill.—I have one question to ask, and a plea to make. Our men—interns, residents, general practitioners—are well prepared and trained in microscopic pathology; they are not well trained in gross pathology. I believe some Kodachrome pictures of these lesions could be collected and shown to our students and young doctors. In ten or fifteen years such a collection would constitute a great contribution.

If anyone wants me to help them in making Kodachrome views of gross pathological lesions, I will be very glad to assist, because I think that is something that needs attention.

DR. GARDINER (Closing).—We, too, are puzzled by the occurrence of cancer of the cervix in an unusually high percentage of these patients.

We studied these cases very carefully but were unable to find any evidence that the vulvar lesions were of metastatic origin. Our conclusion was that these patients had a particular biological affinity for the development of carcinoma.

Any patient with carcinoma of the cervix should receive a very careful vulvar examination.

We particularly avoided the use of "Leukoplakia, Grade I, II, III, or IV." Our concept is that intraepithelial carcinoma is cancer. We believe we should treat it as cancer. Carcinoma may exist in the intraepithelial phase as well as in the invasive phase.

EXPERIMENTAL NONSURGICAL THERAPY OF PELVIC MALIGNANCIES*

A Review

ALLAN C. BARNES, M.D., COLUMBUS, OHIO

WITH the repopularization of radical surgery as a form of therapy for cervical carcinoma about a decade ago,[1, 2] a great many centers undertook this therapy—not, they would protest, because they knew it was better, but because they wanted to find out. The result was that for a time there was a surprising degree of unanimity in our specialty on the investigative work being carried out in the treatment of cervical carcinoma. The centers which had the time, the facilities, and the patients were overwhelmingly engaged in comparing surgical with radiation therapy. The result of this singleness of topic, in turn, was that, on the one hand, the experimental work in the nonsurgical therapy for pelvic malignancies tended to lag behind. And, on the other hand, if one were to approach a gynecologist to determine what studies were being carried out in this specialty in the treeatment of cancer, the chances are that he would cite the re-evaluation of the place of surgery, and would know of no other.

This situation apparently motivated your officers when they assigned the present topic for discussion, and one must immediately recognize the distinct difference between this presentation and others that have preceded it in this series, which is that there is less of immediate usefulness in our everyday office practice in this topic than in any other which has been assigned.

Even Dr. Schmitz's judicious and balanced evaluation last year[3] of the comparative places of surgery and irradiation in the treatment of carcinoma of the cervix contained more material which would be likely to be more immediately useful to more practitioners than this one is likely to contain. Yet saying that this is a topic of scant immediate applicability does not alter the fundamental importance of the subject, because this type of work is now being done, its ultimate applicability is potentially tremendous, and as enlightened specialists—and I trust that we are all that—we should be cognizant of such studies. We should be informed specialists, and we should be informed through such media as this meeting, before our patients are informed through the offices of the *Woman's Home Companion, The Reader's Digest,* and other such "medical journals."

This, then, is informative rather than combative in nature, and one other word should be said by way of introduction: We shall consider here, in sequence, a group of experimental suggestions and trials that have been made in the therapy of pelvic malignancies. Since none of them is five years old, there are

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no five-year cure rates to discuss. But we can survey their nature, discuss their limitations, and tentatively evaluate their place in our therapeutic armamentarium, their potential role in our professional lives.

Cobalt^{60}.—The characteristics of cobalt^{60} are perhaps familiar to all (Table I). It has a half life of 5.3 years, and hence represents a stable investment for the institution. Its residual activity can be "warmed up"; but one should recognize that the only value of this is that it reduces the disposal problem; the old, partially active cobalt does not need to be disposed of, but can be sent back to the nuclear reactor to be brought up to full strength again.

TABLE I. CHARACTERISTICS OF COBALT^{60}

1. Half life of 5.3 years. Residual activity can be "warmed up" in reactor
2. Homogenous gamma radiation—1.1 and 1.3 Mev
3. Soft beta radiation
4. Leakage impossible, no gaseous radioactive daughters
5. Magnetic, facilitates handling
6. Cobalt can be activated in any desired shape at moderate cost
7. Cobalt can be activated in any desired quantity at moderate cost
8. Physiologically inert and nontoxic.

It produces only two gamma rays, one of 1.1 and one of 1.3 Mev value. The beta radiation is exceedingly weak and can be screened out easily. Leakage is impossible. The material is magnetic, and for safety can be handled by a remote control magnet. It can be activated in any desired shape or quantity at moderate cost. It is physiologically inert, and, should it come in contact with the patient, is nontoxic.

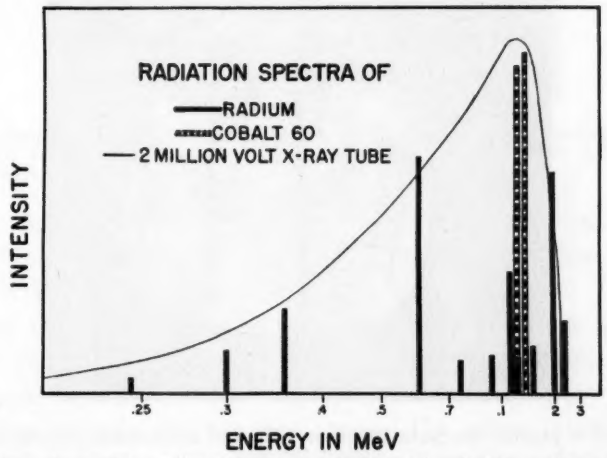

Fig. 1.—Comparative strengths of the gamma radiation of cobalt^{60}, radium and 2 million volt x-ray tube.

Perhaps the most publicized form in which cobalt has been used—although not its commonest use—is as the cobalt "bomb," which takes advantage of the long half life, the strong gamma radiation, and the fact that it can be made in any quantity. There is one cobalt bomb with which there has been any appreciable experience in treating patients.[4] It simply represents a volume of

cobalt approximately the size of a tennis ball, actually activated in sections. It is used to administer a beam of gamma radiation as external therapy.

A comparison between such a bomb and other sources of gamma radiation is indicated in Fig. 1. The curve represents the range of output of a 2 million volt x-ray tube. The solid bars show the gamma radiations from radium; the broken bars represent the gamma radiations from cobalt. It is not unfair to say that the Co^{60} bomb, beaming the rays from a large mass of cobalt, will not achieve anything that could not be achieved by a properly shielded 2 million volt x-ray tube. In other words, this is external therapy of a high voltage type. We must expect nothing of it that could not be obtained with high-voltage external therapy. It will be somewhat limited by skin tolerance, although not as much so as with low-voltage therapy.[5]

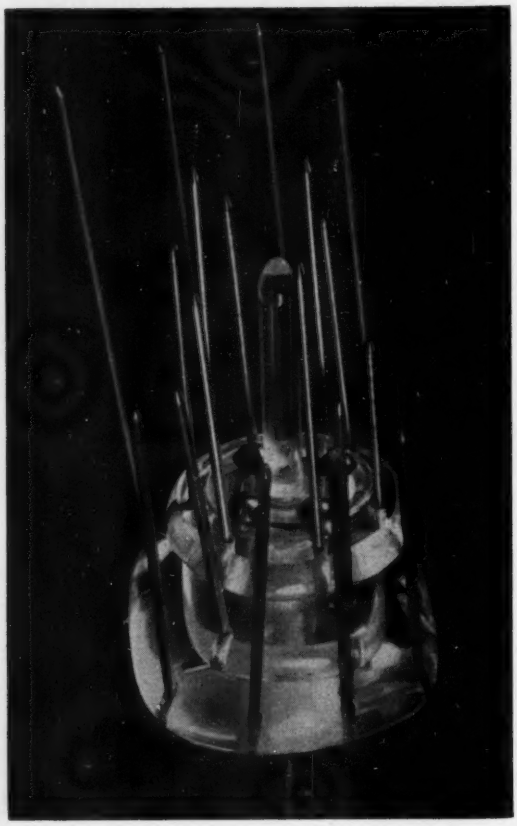

Fig. 2.—Example of a plastic template together with the aluminum needles used for intrapelvic cobalt therapy.

Cobalt has also been used intrapelvically,[6, 7] taking advantage of the fact that it can be handled easily and can be rearranged to suit the individual patient. It does not require heavy shielding and hence fine needles can be constructed for interstitial therapy.

The particular form we have used has involved making plastic molds for the vagina to serve as templates with which the needles can be guided into

their proper places (Fig. 2). The needles are of aluminum tubing, made to measure the day before the patient is to be treated. The combination of needles and templates can produce a blanket of gamma radiation across the pelvis, as indicated by Fig. 3. Such a technique increases the individualization for the particular patient, and takes into consideration the size of the pelvis, the direction of spread of the lesion, and the location of the neoplasm. To the extent that such individualization represents an advantage, a technique with low-intensity, multiple-source cobalt needles, which are tailored to the individual patient and placed precisely through a template guide, has a certain amount to offer.

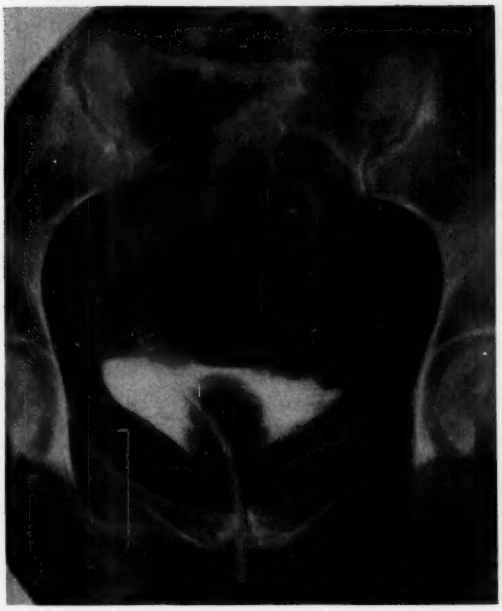

Fig. 3.—Anteroposterior view of pelvis with template and needles in place. Central needles have been reduced in length to lower the dosage where the patient had previously received (inadequate) therapy with radium colpostat and tandem.

In Fig. 4 the source illustrated at the top is the aluminum needle just mentioned. The stainless steel needle (middle drawing) has been used at the University of Arkansas,[8] and there is much to recommend it. However, it is also possible to use the same principle of multiple fine sources in a hollow nylon tubing[9] which can be sewed into the patient at laparotomy, and left in place until the desired dosage is achieved, to irradiate any part of the body.[10, 11] With such nylon threads one can sew around the entire lateral pelvic wall and give a field of irradiation to the nodes as well as the extensions in the broad ligament. Fig. 5 presents illustrative x-ray films of such threads sewed in place.

Of this thread technique, one can say that it is best for a relatively flat field. Three dimensional spaces have been sewed, but the placement is often not as even, and the dosage calculations more difficult. While this technique increases the procedure for the patient by dictating laparotomy, it reduces the

threat of patient injury. There is less chance of bowel and bladder damage when the placement of the radioactive elements is carried out under direct visualization.

Nylon threads containing radioactive sources can and should be readily available. They can be sewed into the patient when an inoperable lesion is discovered, with the ends left exposed through a drain for subsequent withdrawal. This technique represents the extreme in patient individualization.

Whether in the form of the bomb, or as intrapelvic sources, or by some other technique, it is safe to say that cobalt^{60} is a permanent addition to our roentgen-therapy armamentarium. The main advantages it offers are adaptability to the individual patient, and/or the patient's tumor. It must be stressed that this is gamma radiation; if a patient is at tolerance to x-ray and radium, she is at tolerance to cobalt. The tumor that is being irradiated does not distinguish whether the gamma ray that strikes it is coming from radium, cobalt, or from any other source. This, then, is not going to extend any additional therapy to the patient who is at tolerance. Rather, it represents an individualization and a potential way to individualize the patient which is not available if we are harnessed to sources which are regrouped and rearranged only with some hazard and at considerable effort and expense to the institution.

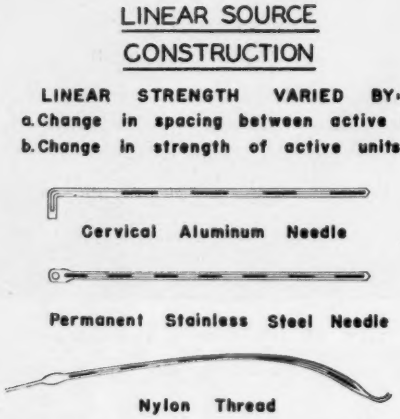

Fig. 4.—Forms of interstitial units available with cobalt^{60}. Any of these types of containers will filter out the beta ray.

Gold^{198}.—The characteristics of radioactive gold (Table II) are in sharp contrast to those of cobalt. It has a half life that is exceedingly brief, 2.7 days, which immediately presents dosage and transportation problems. It produces only one gamma ray, which is soft, and it has a beta ray which is comparatively strong. As with the other metals, leakage is impossible. In a finely ground state it is easily handled in colloidal solution. Gold can be activated in any desired shape, at an exceedingly moderate cost, and in any quantity. It is also physiologically inert, and can be successfully injected into the body.

Taking advantage of some of those characteristics, Sherman[12, 13] and his group in St. Louis have introduced the interstitial injection of colloidal gold mixed with pectin. The injection is made directly into the parametrial tissues; the

active particles are picked up in the lymphatics and carried to the nodes. There is perhaps no more logical way of reaching the pelvic nodes than to have the lymphatics carry the irradiation there.

This contribution undoubtedly is one of the most ingenious and one of the most interesting methods of getting irradiation to the lateral pelvic wall. It represents both beta and gamma therapy, since both rays will strike the tissues involved, but its physics is not precisely controllable. One cannot predict exactly how much activity is going to end up in any given node, and must

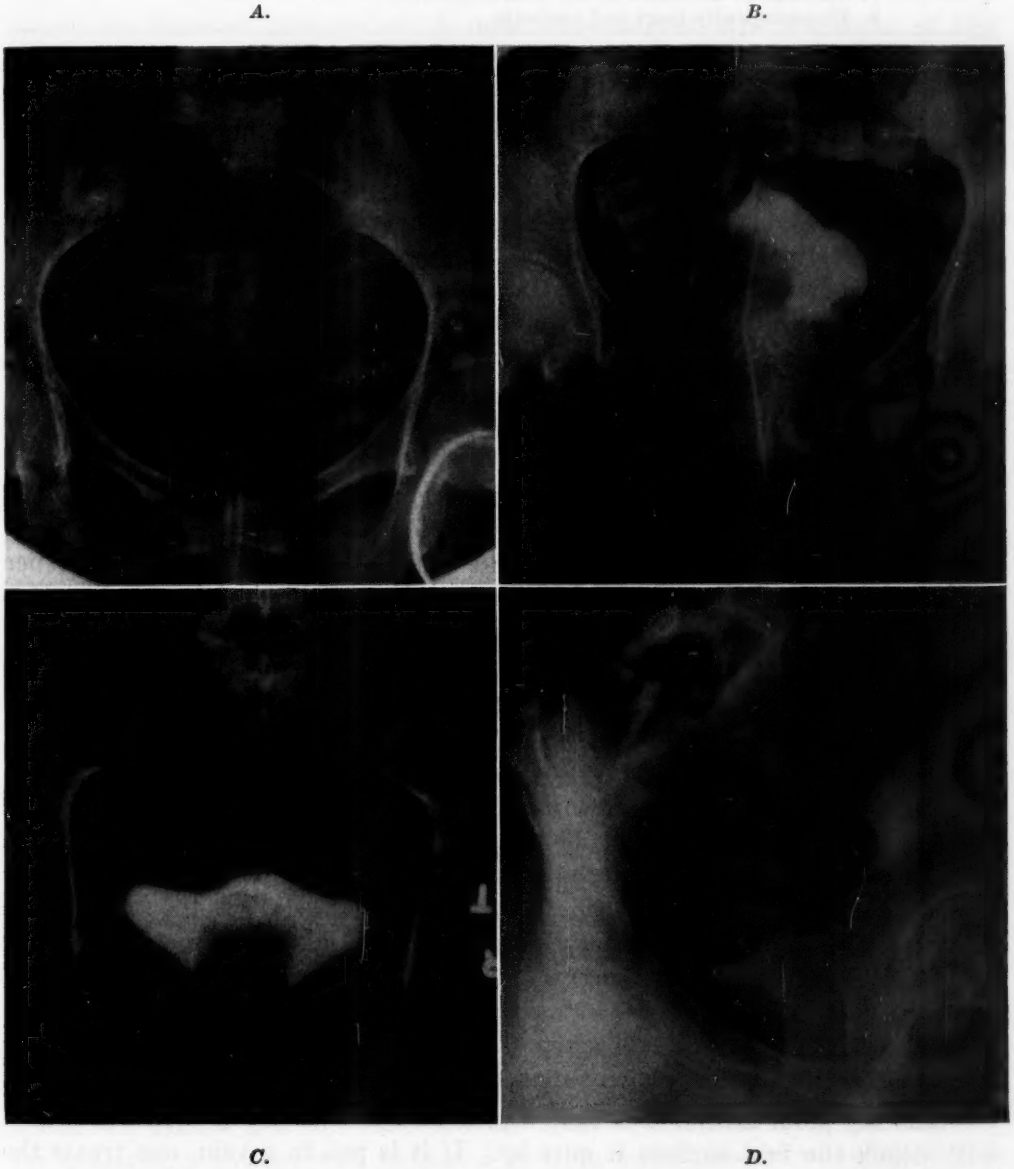

Fig. 5.—Pelvic x-rays of patients with nylon threads sewed in place. *A*, Placement with active elements over nodes on side wall of pelvis. *B*, Threads sewed extraperitoneally from space of Retzius to vagina to bring active elements into a periurethral recurrence. *C*, Threads sewed over lateral wall and into base of broad ligament in a League of Nations II cervical carcinoma. *D*, Oblique view, same patient.

calculate it as millicuries per gram of tissue, approximating it somewhat and recognizing that the activity is declining rather rapidly as the particles move toward their goal.

TABLE II. CHARACTERISTICS OF GOLD^{198}

1. Half life of 2.7 days. Some dosage and transportation problems.
2. Single gamma radiation of 0.44 Mev
3. Beta radiation of 0.9 Mev
4. Leakage impossible, no gaseous radioactive daughters
5. In finely ground state makes easily handled collodial solution
6. Gold can be activated in any desired shape at moderate cost
7. Gold can be activated in any desired quantity
8. Physiologically inert and nontoxic

Gold administered intraperitoneally to the patient with ovarian carcinoma is considerably more familiar to most of us.[14] Here one is relying chiefly on the beta radiation. Obviously, radioactivity that could penetrate through the wall of the intestine cannot be placed intraperitoneally, or one would get severe intestinal burns. Actually, the penetrability of the rays is about 0.4 mm. In other words, in these circumstances gold^{198} does not treat the tumor; it is simply administered for its superficial sclerosing action on the peritoneum, to reduce the ascites that the patient has. It is pure palliation, and as such does not significantly influence the growth of the lesion at all.

Incidentally, except for the mechanical difficulties, gold is usable for its gamma therapy. It requires shielding, to eliminate the beta ray, and hence presents problems in rapid handling. If the sequence from activated gold in the nuclear reactor to shielded gold in the patient can be achieved in 24 hours, every 100 mc. of gold that starts will yield about 75 mc. when implanted. A filter of 2 mm. of nonradioactive gold will filter out approximately 95 per cent of the beta ray of the radioactive gold. Hence a fine wire of radioactive gold put in a small capsule would permit us to use the relatively soft gamma ray for gamma-ray therapy. It has a very limited application at the present time; no institution is doing it consistently. We have tried it as an exercise in radioactive logistics more than as a consistent weapon in our armamentarium.

Intra-arterial Nitrogen Mustard.—In a survey of the literature it is not easy to determine who first made the fundamental observation that nitrogen mustard injected into the arterial system has a totally different effect from mustard applied on the venous side. Klopp,[15] at Bethesda, was the first to work it out in any detail, and, certainly, in so far as the histologic impact of intra-arterial nitrogen mustard is concerned, his is the best evidence; he and Cromer[16] have the only published series of cases of cervical carcinoma treated by intra-arterial nitrogen mustard. This report, plus 20 patients we treated about two years ago, represents our entire contact with the technique.

The key point is this: Nitrogen mustard administered into the blood stream will attack the first surface it goes by. If it is put in a vein, one treats the bone marrow and the pulmonary system. If it is put into the arterial side, it will go into the first epithelial surface that it passes on being distributed through the capillary bed. That immediately means that the gynecologist

should be interested in it, because the arterial system to the pelvic malignancies is relatively localized, and readily accessible.

Fig. 6 indicates the fluoroscopic landmarks for arterial catheter placement. The aorta can be approached through the left brachial artery or, as we have been more inclined to use it, through the femorals, passing the catheter in retrograde fashion. At T_{10} the mustard will strike the intestinal, the splenic, and liver circulations. It is impossible to reach the ovarian arteries without administering the mustard to the renal circulation (L_1). However, at the bottom of L_3 or the top of L_4, the catheter is almost invariably below the inferior mesenteric. A dose administered into the aorta at this point attacks by far the greater part of the pelvic circulation. The patient can take up to 1.5 mg. of nitrogen mustard per kilogram of body weight intra-arterially, whereas she can take only 0.1 to 0.2 mg. per kilogram intravenously.

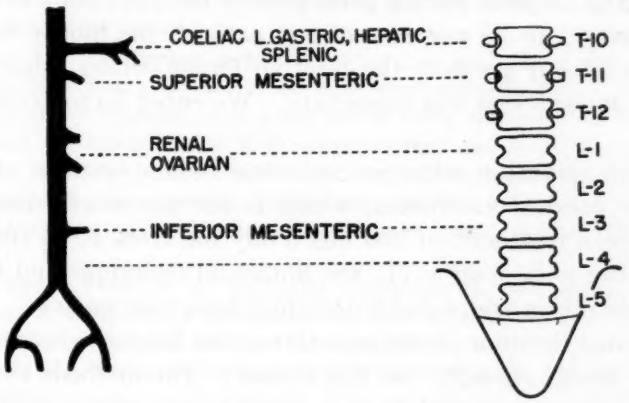

Fig. 6.—Fluoroscopic spinal landmarks for the major arteries of the abdomen.

We have had a few patients to whom we have given no other therapy than nitrogen mustard, simply to follow the tissue effect. It produces the same cellular picture that irradiation does, and in sequential biopsies the pathologist soon starts reading "irradiation effects"—tissue swelling and nuclear destruction.

Cromer and Klopp, in their series, irradiated their patients with less than a full cancerocidal dose prior to the administration of the nitrogen mustard. From some preliminary animal work we have been carrying out, we are suspicious that intra-arterial nitrogen mustard compounds with irradiation, and cannot be used in a patient who is at radiation tolerance—or at least in these patients should be used circumspectly. While this must for the moment remain a suspicion rather than a fact, it is a strong enough suspicion that at present we are consigning those people to intra-arterial nitrogen mustard in whom we cannot get full cancerocidal doses of irradiation—predominantly, for example, a patient with extensive ovarian metastasis, in whom the roentgenologist can deliver to the midabdominal plane from 2,000 to 3,000 gamma roentgens. This dose leaves the malignancy grossly undertreated. Intra-arterial mustard is a weapon which could be used in such a situation.

Intravenous Progesterone.—There is one other form of therapy that has been more recently introduced, but perhaps not quite as widely discussed. In 1951 Hertz[17] suggested the use of progesterone in cancer of the cervix, and has reported the histologic changes in squamous-cell cervical carcinoma after massive doses of progesterone. The recommended minimum dose is 250 mg. of progesterone a day, and many of the courses lasted up to 100 days.

Furthermore, since the maximum solubility of progesterone is 50 mg. per cubic centimeter of oil, a 100 day course would require the administration of 500 c.c. of intramuscular oil, with the attendant threat of oil abscess, sensitization, and encapsulated oil. Within the past year, however, a simple method for administering the steroids intravenously has been devised by Rothchild.[18] Armed with this, we[19] recalled our patients with cervical carcinoma, and now have a group of about 20 of them who have had up to 500 mg. a day of intravenous progesterone.

On sequential biopsies during progesterone therapy, there is a tissue change in the malignancy. In 25 per cent of our patients the biopsy turned negative. In 33 per cent of our patients the positive Papanicolaou smear was reversed. The negativity in each case was temporary. We cured no patients. Hertz cured no patients.

The present situation with progesterone is simply this: It does have a tissue effect on cervical carcinoma, which is not necessarily cancerocidal. Its dosage should be a minimum of 250 mg. a day for from 10 to 100 days. Therefore, if it is going to be used at all, the Rothchild technique and the intravenous route of administration are probably the chief hope that we have.

Why does one continue to use something that has no cancerocidal impact on the neoplastic tissue? Simply for this reason: The methods that we have discussed in this review, reported from a great many centers, and those tried by us, are all advances in the treatment of cancer. But one should remember that advances in the treatment of cancer have nothing to do with the cure of cancer. The cure of cancer is not going to come by more extensively cutting it out, or by more severely burning it. The cure for cancer will probably come from the biochemists, from some "normalizing principle" given systemically that will restore the body's ability to control and regulate its cellular growth. From such a point of view intravenous progesterone offers a research avenue of more than average interest.

The other techniques which we have here considered are the weapons we are going to have to use between now and that indefinite date when our unknown biochemical friends find a cure. They are the experimental advances in the treatment of pelvic malignancies of the past few and perhaps the next many years.

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Discussion

DR. BARNES (Closing).—I would like to point out that it would be well if we had gold wire available at the time of some operations. We operate upon a patient and find positive nodes where we never expected them. While the abdomen is open, why not put gold wire into those nodes? It is inert; it has a half life of 2.7 days; nine days later its activity will be almost exhausted.

There comes the transportation problem—the gold isn't there and active on the day you perform the operation. Or the institution must arrange for X amount of gold to arrive each Wednesday morning, and everyone in town will have to schedule operation upon the potential malignancies for Wednesday, so they can leave the solution behind, or the wires will be available when needed. In general the use of gold^{198} requires the rescheduling of patients for a second laparotomy (wires) or a tap (colloidal solution). Until the day comes that we are activating our own gold, logistics will be the greatest problem.

One advantage I know in the gold and transportation problem is the fact that you can send your patient home with a radioactive abdomen without too much harm. By the time the needle hole is well sealed, by the time the incision that was used for the catheter is well sealed, the radioactivity has gone downhill to the extent that she will not expose family or friends unnecessarily.

RELATIONSHIPS OF THE FEMALE URETHRA AND BLADDER IN URINARY STRESS INCONTINENCE*

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(From the Department of Gynecology and Obstetrics, Henry Ford Hospital)

URINARY stress incontinence in women is a problem without precise definition. Clinical evidence suggests that alterations in the relationship of the urethra and bladder play an important role in female stress incontinence. This report is to present results of a modified urethrocystographic technique which permits radiographic demonstration of the bladder outline and the entire undistorted urethra.

Instead of a semirigid catheter, a metallic bead chain, of the type commonly used for carrying keys, was used to study urethral configuration. The method has the advantages of simplicity, accuracy of detail, freedom from distortion, and excellent roentgenographic contrast in both the anteroposterior and lateral positions.

Method

The apparatus consisted of the usual instruments necessary for female sterile catheterization. The bead chain measured 25 cm. in length. The metallic beads were 3 mm. in diameter and were separated by connecting rods 1.5 mm. in length. For insertion of the chain, a No. 18 French, soft rubber catheter was bisected longitudinally and the chain laid in the lumen. Sixty c.c. of 15 per cent Skiodan was instilled into the bladder after insertion of the chain. All patients were studied in the standing position. Urethrocystograms were taken with the patient in the anteroposterior and lateral positions using usual radiographic technique. Pictures were taken in each position with the patient at rest. She was then asked to strain and the pictures were repeated. When an operation was performed, pre- and postoperative studies were done.

The procedure for insertion of the chain was easily learned. The patient was draped as for sterile catheterization. The bead chain was fitted into the inside lumen of the bisected catheter with the first bead extending over the catheter tip (Fig. 1). The entire catheter was lightly lubricated with jelly and inserted into the urethra for a distance of 12 cm. To disengage the chain from the catheter, the external end was held taut as the catheter was further introduced. This maneuver liberated the chain from the catheter which could then be withdrawn leaving the chain in place in the urethra and bladder. The bladder was emptied of urine with a glass catheter and 60 c.c. of 15 per cent Skiodan was instilled.

Material

A large variety of patients were studied. The first group was made up of normal nonparous and parous patients. The second group was made up of continent parous patients demonstrating loss of mechanical support of the

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bladder floor. The third group was made up of patients suffering from urinary stress incontinence.

Urethral configuration and bladder outline were sharply detailed in both the anteroposterior and lateral positions. The dynamic effects of straining were well demonstrated, and the altered relationships of the urethra, bladder and symphysis pubis were easily compared (Fig. 2).

For the purpose of this report, all film details were eliminated except the bladder, urethra, and symphysis pubis. These structures were traced by the medical artist to thin tissue paper and transferred to appropriate contrast paper for photographing.

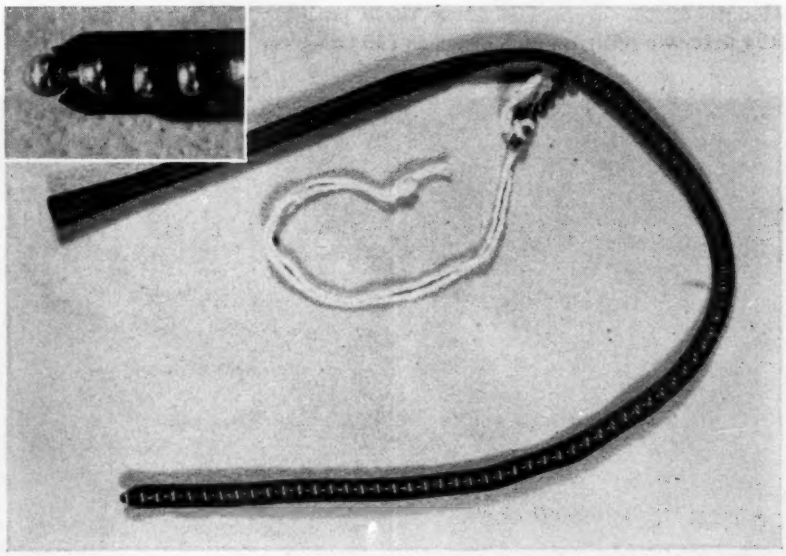

Fig. 1.—Demonstration of the metallic bead chain in the lumen of the catheter.
The close-up photograph, in the upper left corner, shows how the tip of the catheter was fashioned to accommodate the connecting rod between the first and second beads. For insertion, the metallic bead chain is laid into the lumen of the catheter with the first bead extending over the tip of the catheter.

Group 1. Normal Asymptomatic Patients

CASE 1.—A. Z., No. 504217, aged 14 years, was the youngest patient studied. She was selected for illustration because she was without urinary symptoms and because pelvic examination demonstrated an intact hymen. (Fig. 3.)

CASE 2.—M. T., No. 659064, aged 23 years, had been married two years. There was no history of pregnancy and the cervix was nulliparous. Because of the similarity of the urethrocystographic relationships, these two patients were considered together.

In the anteroposterior position the bladder shadow tended to be ovoid. The inferior border was located at the midpubis. The urethra was located in the midline.

The lateral views demonstrated the anterior third of the bladder to lie over the symphysis. The urethra ran obliquely forward from the base of the bladder in a rather straight line to the distal end where it curved downward. If, on the lateral views, the bladder were divided into thirds, the internal urinary meatus was located at the junction of the posterior and middle thirds.

Straining caused little alteration in the urethrovesical relationships although there was suggestive evidence in one patient that the bladder rotated forward and downward toward the pubis. Slight descensus of the bladder floor to the level of the lower third of the symphysis was evident and the superior bladder surface became somewhat flattened.

CASE 3.—M. R., No. 610637, aged 46 years, para ii, complained of no urinary symptoms and demonstrated no loss of mechanical support to the bladder floor as the result of parturition. (Fig. 4.) When compared with nulliparas, the anteroposterior views of this patient demonstrated the bladder to be flattened. The relative position of the bladder floor with the symphysis revealed no loss of support.

The effects of parturition were evident in the lateral views. Loss of posterior bladder support resulted in elongation of the anteroposterior diameter of the bladder. This caused the internal urinary meatus to be located at the midplane of the bladder floor.

The effects of straining were best shown on the lateral views. Straining caused slight funneling downward of the internal urinary meatus which was located at the most depressed portion of the bladder floor.

The length of the urethra in these three patients was approximately 10 beads (40 mm.) for the first two patients and 12 beads (48 mm.) for the third patient.

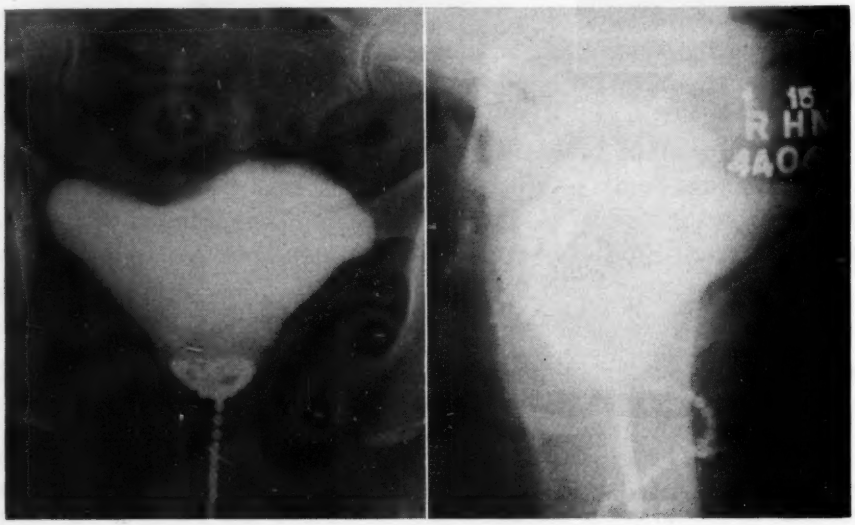

Fig. 2.—Roentgenograms showing detail of the urethrocystograms obtained with the use of the metallic bead chain and 15 per cent Skiodan. The metallic marker designating the level of the external urinary meatus is evident for measurement of urethral length.

Group 2. Loss of Mechanical Support of Bladder Floor

Two patients having no symptoms of urinary stress incontinence were selected for demonstration of the effects of loss of mechanical support to the bladder and to the urethra caused by parturition.

CASE 4.—A. I., No. 648723, aged 62 years, mother of two children, complained of symptoms referable to a large cystocele.

Preoperative Urethrocystograms.—Urethrocystograms taken in the anteroposterior position demonstrated the bladder to be located at a considerably lower level than normal. Straining caused the bladder to be further displaced to a lower position. The major loss of support appeared to be in the midline as the inferior bladder walls sloped downward toward the internal urinary meatus.

The lateral films disclosed alterations in the urethrovesical relationships. The base of the bladder was conical in the nonstraining films. The internal urinary meatus was at the apex of the inverted cone located in the midbladder plane. Straining demonstrated backward and downward rotation of the bladder. As the result of this action, the internal urinary meatus was assimilated into the anterior bladder wall. It was located at a level above the most depressed portion of the bladder base. The length of the urethra was 12 beads (48 mm.).

Operation.—The operation performed upon this patient was anterior colporrhaphy.

Postoperative Urethrocystograms.—The anteroposterior films, when she was not straining, demonstrated the bladder to be located at a higher level. Straining caused slight descensus of the bladder floor.

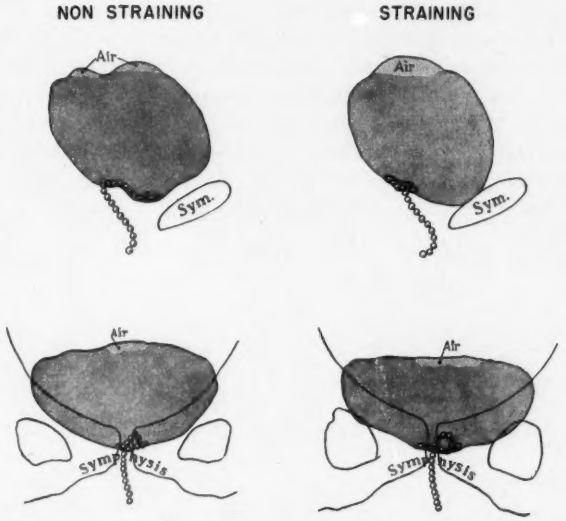

Fig. 3.—Shows the bladder shadows in a 14-year-old normal virgin.

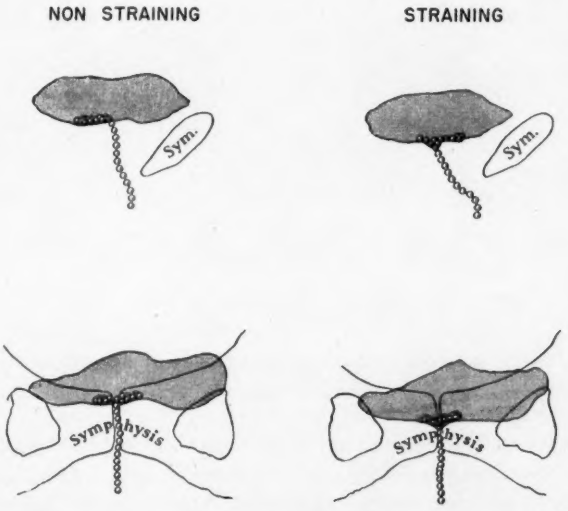

Fig. 4.—Shows the bladder shadows in a 46-year-old multipara. There is no evidence of disturbance of bladder support.

The lateral films also showed the bladder to be located in a normal position. The anterior third of the bladder was situated above the symphysis and the internal urinary meatus joined the bladder near the junction of the posterior and middle thirds. The internal urinary meatus was located at the most depressed portion of the bladder floor and the urethral configuration resembled normal. The length of the urethra was increased by the operative procedure and measured 14 beads (54 mm.).

Clinical Result.—The clinical result was restoration of support to the bladder floor. The patient was without urinary symptoms.

CASE 5.—B. C., No. 225301, aged 42 years, para iii, demonstrated urethrocystographic findings in uterine prolapse. (Fig. 5, *A* and *B*.) Her urinary symptoms were those of excessive continence. To empty the bladder, she found it necessary to replace the prolapsed uterus.

Preoperative Urethrocystograms.—The anteroposterior nonstraining films disclosed the bladder level decidedly low. Straining caused marked descensus of the bladder.

The lateral nonstraining fims showed the superior surface of the bladder to be flattened. The inferior borders sloped downward to the internal urinary meatus. When the patient strained, the bladder rotated backward and downward. Because the general position of the urethra changed but little as the result of straining, the internal urinary meatus was assimilated into the anterior bladder wall and was located high above the most depressed portion of the bladder floor. The course of the urethra was tortuous. The length of the urethra averaged 16 beads (63 mm.).

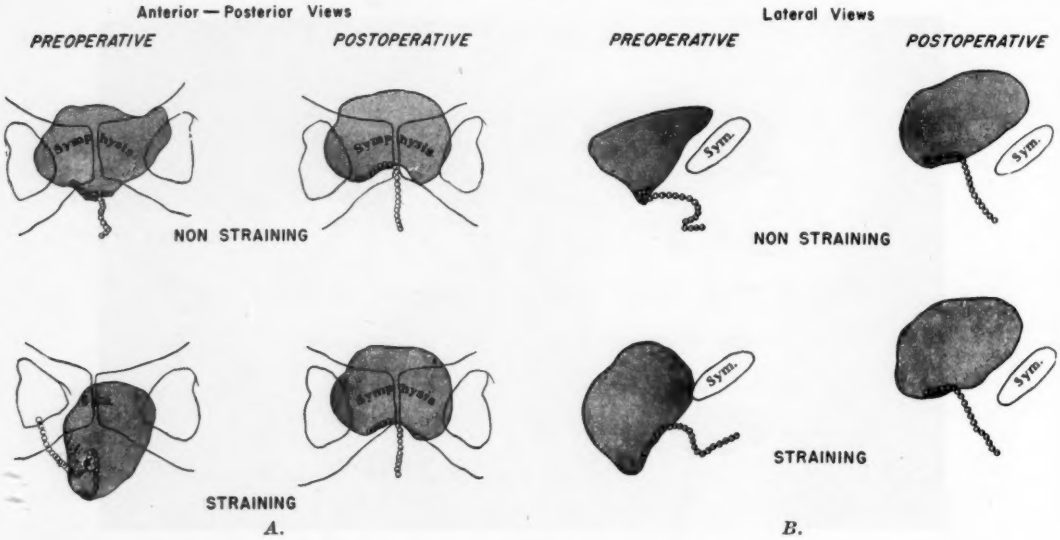

Fig. 5.—Shows the bladder shadows in association with prolapse of the uterus and the return to the normal by vaginal operation.

Operation.—The operation consisted of vaginal hysterectomy with repair of the cystocele and rectocele.

Postoperative Urethrocystograms.—The postoperative anteroposterior nonstraining films showed the bladder to be located considerably higher than before operation. Straining caused little descensus.

The lateral films showed the bladder to occupy a position that compared favorably with normal in both the nonstraining and straining phases. The internal urinary meatus assumed a normal position and the course of the urethra was straightened.

Clinical Result.—The postoperative clinical result demonstrated a well-supported bladder floor and the patient was without urinary symptoms.

Group 3. Urethrovesical Relationships in Urinary Stress Incontinence

Four patients were selected for demonstration of the urethrocystographic findings in urinary stress incontinence.

CASE 6.—L. M., No. 412732, aged 44 years, para i, was operated upon using the Kennedy procedure. (Fig. 6, *A* and *B*.)

Preoperative Urethrocystograms.—The anteroposterior films taken when the patient was not straining showed the bladder to be located in an approximately normal position.

The bladder floor sloped gradually downward to the internal urinary meatus. Straining caused descensus of the bladder and the base assumed a pointed appearance.

The lateral films disclosed the bladder base to be conical. The internal urinary meatus was located at the apex of the inverted cone in the midbladder plane. Straining caused the bladder base to plunge downward in a vertical direction with little alteration in the relation of the internal urinary meatus with the bladder base. As the result of this action, the internal urinary meatus was displaced to the most dependent bladder level. The urethra averaged 11 beads (44 mm.).

Operation.—The Kennedy operation was used for this patient.

Postoperative Urethrograms.—The postoperative anteroposterior nonstraining films disclosed the bladder floor to be well supported. From observation of the lateral films, a considerable portion of the bladder was seen to occupy the suprapubic area. The urethra was well supported. Straining caused little descensus of the bladder and urethra, although slight backward and downward rotation of the posterior end of the bladder base was evident on the lateral films.

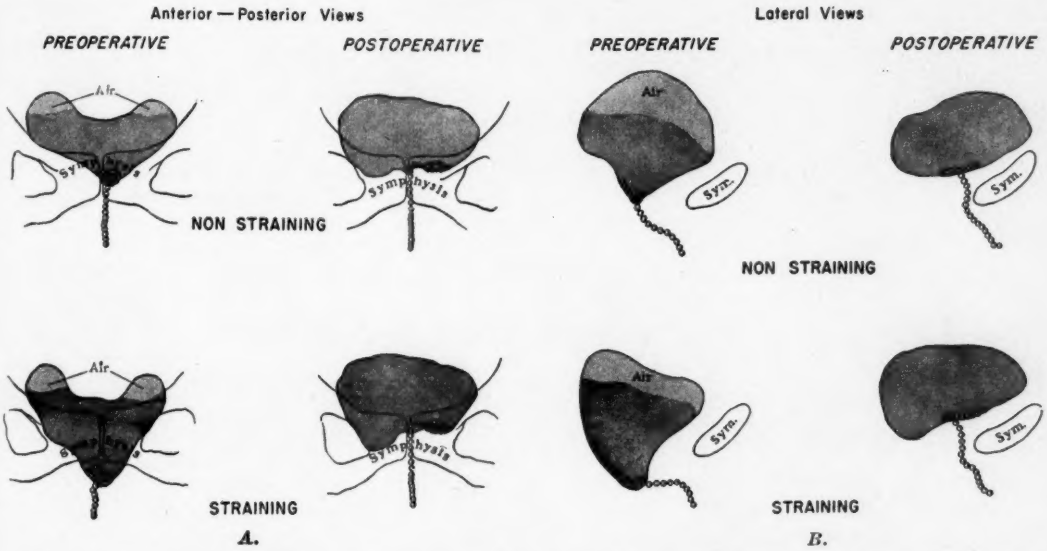

Fig. 6.—Shows the bladder in a patient with urinary stress incontinence associated with a cystocele corrected by the Kennedy procedure.

The shape of the bladder was changed by operation. Before operation the vertical diameter of the bladder was lengthened. Through operative support of the bladder floor the vertical diameter of the bladder was decreased. The urethra was elongated as the result of operation and measured 15 beads (60 mm.).

Clinical Result.—The clinical result was complete restoration of urinary continence.

CASE 7.—D. B., No. 652609, aged 36 years, para iv, complained of urinary stress incontinence. Her clothing was constantly wet. She was operated upon using the Marshall-Marchetti operation.

Preoperative Urethrocystograms.—Urethrocystographic evidence of failure of support to the bladder base was less pronounced in this patient. The anteroposterior, nonstraining films showed the bladder location to be normal. Straining caused the bladder floor to assume a pointed appearance. The lateral films, when the patient was not straining, appeared quite normal. However, when the patient strained, the bladder descended vertically. Rotation downward and backward did not occur. The configuration of the urethra appeared normal and the urethral length was 16 beads (63 mm.).

Operation.—The Marshall-Marchetti operation was used for this patient.

Postoperative Urethrocystograms.—Considerable alteration in the urethrovesical relationships resulted. Elevation of the bladder was noted on the anteroposterior films with little loss of support demonstrated by straining. The lateral films showed the bladder to be rotated backward. The internal urinary meatus was located high on the anterior bladder wall with the most dependent bladder level considerably below this point. Straining increased the backward and downward rotation of the bladder in its relation with the urethra. The urethra was almost vertical in position. It measured 16 beads (63 mm.).

Clinical Result.—The clinical result was complete relief of urinary incontinence.

CASE 8.—M. B., No. 440668, aged 67 years, para i, complained of severe urinary stress incontinence. She was selected for demonstration because there was little evidence of cystourethrocele on vaginal examination; however, the urethrocystographic studies revealed considerable loss of support. (Fig. 7, *A* and *B*.)

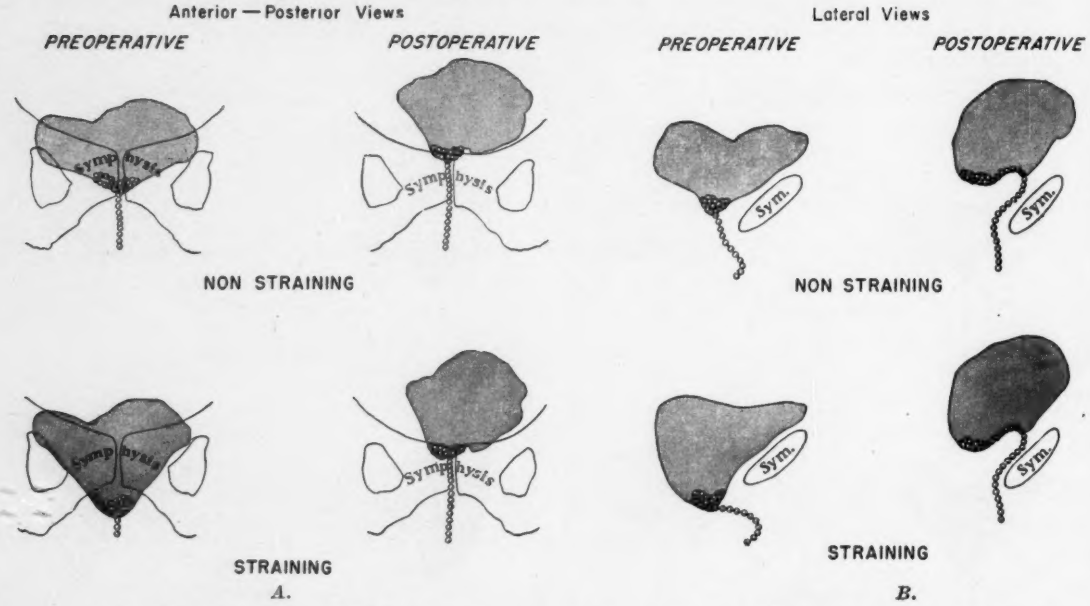

Fig. 7.—Shows the bladder shadows in a patient with urinary incontinence but little evidence of cystocele and the correction by retropubic fixation of the anterior vaginal wall (Marshall-Marchetti operation).

Preoperative Urethrocystograms.—In general, the urethrocystographic findings in this patient duplicated those of L. M., Case 6. In the anteroposterior films, the bladder position was located somewhat lower than normal. The walls of the bladder base sloped downward with the internal urinary meatus located at the apex of the angle formed by the converging walls. On the lateral films, the internal urinary meatus was located near the midplane of the bladder base.

Upon straining, the bladder was observed to descend in the vertical direction. The base was cone-shaped and the internal urinary meatus was located at the most dependent bladder level.

Operation.—The operation used for this patient was the Marshall-Marchetti procedure.

Postoperative Urethrocystograms.—Postoperatively, the anteroposterior urethrocystograms demonstrated considerable elevation of the bladder and urethra. The lateral films revealed the urethra to be vertically placed. Considerable bladder volume occupied the suprapubic area. Straining caused slight descensus. The lateral films showed the internal urinary meatus to be elevated to a high position on the anterior bladder wall. Straining caused downward and backward rotation of the bladder in relation to the fixed urethra.

Clinical Result.—The clinical result was complete restoration of urinary continence.

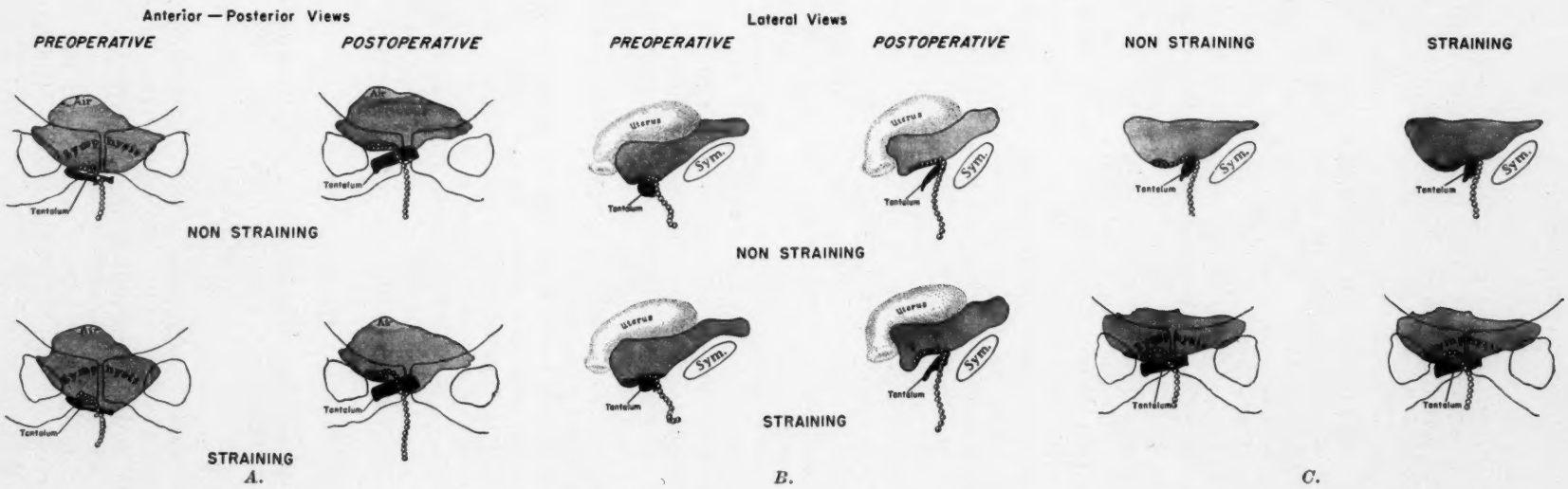

Fig. 8.—Shows the bladder shadows in a patient with persistent incontinence of urine despite 4 vaginal operations and the partial correction (*B*) by retropubic fixation of the anterior vaginal wall and a further correction (*C*) by an abdominal operation.

CASE 9.—L. W., No. 518641, aged 40 years, para iv, represents a patient with persistent urinary incontinence after repeated efforts to correct the condition. Four vaginal plastic operations had been performed; all were unsuccessful. At the last attempt a piece of tantalum had been sutured beneath the urethrovesical junction for added support. When this failed to relieve the patient, the ureters were transplanted into the rectum. Chronic azotemia resulted. This required left sigmoid colostomy.

When first seen at Henry Ford Hospital, the patient demonstrated a well-functioning colostomy and a rectal bladder. Injection of saline solution into the bladder demonstrated bladder incontinence. This sequence of events had resulted in a broken marriage and a miserable patient. (Fig. 8, *A*, *B*, and *C*.)

Preoperative Urethrocystograms.—The anteroposterior films demonstrated the bladder position to be low. The lateral films demonstrated a bladder of peculiar shape. This peculiarity was caused by pressure from an acutely anteverted uterus fixed in this position by a technically successful uterine suspension operation. As a result of this, the bladder capacity was small. The tantalum plate distorted the contour of the bladder base and was located posterior to the urethrovesical junction. The internal urinary meatus was located at the junction of the posterior and middle thirds of the bladder at the most dependent bladder level. Straining caused further descent of the bladder and urethra.

Operation.—The Marshall-Marchetti operation was used for this patient.

Postoperative Urethrocystograms.—The anteroposterior films showed elevation of the bladder and urethra. On the lateral films the urethra was observed to assume a vertical position. The imprint of the superimposed uterus on the superior bladder wall was still seen. The internal urinary meatus was displaced anteriorly near the midplane of the bladder.

Straining caused slight descensus of the bladder with little alteration in the position of the urethra. The posterior portion of the bladder base descended to a lower level than the internal urinary meatus as observed on the lateral films. Posterior rotation of the bladder appeared to be limited by the fixed uterus. The urethral length was increased by operation from a preoperative measurement of 12 beads (48 mm.) to 15 beads (57 mm.).

Clinical Result.—Following operation, the patient could hold 150 c.c. of saline solution for 12 hours without incontinence. The bladder capacity was limited and volumes greater than this caused overflow incontinence. The ureters were then united by Dr. A. W. Bohne of the Division of Urology and the sigmoid anastomosed by Dr. James Barron of the Department of General Surgery. The uterus was removed to improve bladder capacity and to allow backward and downward rotation of the bladder.

The final urethrocystograms revealed considerable alteration in the urethrovesical relationships. These changes were most evident on the lateral films. A more normal bladder contour was noted. The urethrovesical junction was located anterior to the midbladder plane because the bladder was free to extend posteriorly.

Straining caused a minor amount of backward and downward rotation of the bladder.

The internal urinary meatus was located at a level higher than the most depressed portion of the bladder. The bladder capacity was increased to normal volume.

Comment

Because knowledge of the physiology of micturition is incomplete, many inconsistencies exist in relating the mechanical status with functional symptoms. Deficiencies in technical methods of investigation have, in part, contributed to lack of understanding of bladder function.

Johanson[1] noted that Cunningham in 1910 first reported roentgen examination of the urethra with the aid of contrast medium. He analyzed methods of cystourethrography and recommended use of a viscous, resorbable, opaque substance in a special contrast combination.

As mentioned by Johanson, contrast media used for demonstrating the urethra have been devised for two different reasons. One group was used for

study of the anatomical changes of the urethra while the other group studied physiological changes. In the investigation of urinary stress incontinence in women, both techniques have been used.

Muellner,[2] and Millin and Read[3] studied the physiology of micturition using a liquid contrast medium for demonstration of the urethra and bladder. They obtained excellent detail of the bladder shadow and the vesical neck. The details of the urethra were vague and incomplete. Muellner's fluoroscopic studies revealed that in the normal nullipara, upon coughing, the base of the bladder did not yield to the increased intra-abdominal pressure which was dissipated along the dome and sides of the bladder.

Voiding efforts were characterized by descent of the bladder neck to the most dependent portion which assumed a pointed appearance. Inhibition of micturition resulted in the bladder neck being pulled up to a higher level than before the micturition effort.

By comparison, in the continent parous patient, the bladder was more relaxed but the neck was not distorted by weakness.

Muellner demonstrated that the incontinent multipara showed considerable excursion downward of the bladder base on coughing and that the internal sphincter took up most of the downward thrust and yielded more than the base. Muellner's studies did not explain why patients with maximum failure of support, those with uterine prolapse, failed to have stress incontinence or why incontinence occasionally occurred after satisfactory anatomical repair of a continent patient with cystocele or uterine prolapse.

A metallic bead chain was used by Barnes for determining urethral configuration in his clinical and investigative review of the fundamental factors in the pathologic physiology of stress incontinence. Barnes'[4, 5] studies were designed to evaluate the physiological effectiveness of the internal urethral sphincter. His use of the metallic bead chain served to mark the course of the urethra as suggested by Stevens and Smith.[6] Barnes studied patients in the anteroposterior and 45 degree oblique views. He emphasized that there was a striking difference between the x-ray picture and the clinical impression in evaluating patients with urinary stress incontinence. Also sphincterometric evaluation did not provide conclusive evidence of the underlying pathology in patients so afflicted.

Ball[7] used a modified No. 18 French Foley catheter for study of the urethra in his work on topographic urethrography. He noted that following parturition there was a tendency for the urethra to be slightly more anterior and inferior to the symphysis than in the nullipara. He stated that continent women with relaxation and prolapse showed good paraurethral support. He also noted that the relaxation of the vaginal walls was posterior to the bladder neck in continent multiparas.

When stress incontinence was present, Ball, Douglas, and Fulkerson[8] stated that there was displacement of the bladder neck forward and downward in relation with the symphysis. This resulted in an accordian effect on the inner third of the urethra and a funneling of the bladder neck.

Using the bead chain technique, they demonstrated no shortening of the urethra in patients with urinary stress incontinence. The accordian effect noted by Ball and associates[8] possibly was caused by the rigidity of the catheter which was used for demonstration of the urethra. Straining apparently telescoped the urethra onto the semirigid catheter, giving the impression of shortening.

Ball[7] and Ball and co-workers[8] studied patients in the horizontal position. The importance of erect patient posture in the study of stress incontinence was emphasized by Berkow,[9] when he pointed out that another name for stress incontinence was orthostatic incontinence. He stated that, theoretically, stress

incontinence could occur whether the patient was erect or in the horizontal position. From a practical standpoint, he noted, it seemed that the horizontal position, by removing the effects of gravity and perhaps also by changing the position of the bladder, so reduced the forces of propulsion that true stress incontinence rarely occurred when the patient was lying down. The bead chain technique permitted more latitude in patient mobility and all patients were studied in the standing position.

Roberts,[10] reviewed the various methods used for urethrography. He adopted Malpas' suggestion of using an old, soft, repeatedly boiled rubber catheter. He concluded that stress incontinence was associated with loss of the posterior urethrovesical angle. The continent multipara demonstrated preservation of this angle. In analysis of operations for repair of urinary stress incontinence, Roberts stated that the success of both anterior colporrhaphy and Aldridge's fascial sling operation depended upon elevation of the urethrovesical junction and restoration of the posterior urethrovesical angle.

Based upon the clinical observation that the anterior two-thirds of the female urethra was not necessary for urinary control,[11, 12] several investigators have directed their attention to the bladder and the bladder neck. Marchetti[13] studied the bladder roentgenographically and concluded that success of the Marshall-Marchetti operation depended upon support to the vesical sphincter mechanism located in the bladder neck and the inner third of the urethra. The anatomical studies of Krantz[14] supported Marchetti's conclusions. When the urethra was studied by Marchetti, liquid medium was used and comparative detail with all forms of bladder-floor relaxation was not complete.

With the metallic bead chain technique the entire urethra could be studied. Urethral outline was undistorted and urethral mobility unrestricted. Roentgen contrast was excellent. Patients were studied in the standing position for demonstration of maximum effects of stress. Although the method was deficient in that it failed to show urethral mucosal pattern, for the study of urinary stress incontinence this feature appeared of little importance.

Standardization of technique for comparison of the entire urethra, bladder, and symphysis pubis was established for study of anatomical changes noted in Groups 1, 2, and 3.

Group 1.—The urethrocystographic studies of a normal group of patients demonstrated the bladder floor to be at the midpubic level. The general shape of the bladder was ovular. The floor was well supported and, although not flat, showed no downward thrust upon straining.

The internal urinary meatus was located near the junction of the posterior and middle thirds on the lateral films. After parturition, when there was no apparent loss of support, the bladder was elongated posteriorly and the internal urinary meatus was located at the midbladder plane. The urethra extended obliquely forward in a straight line. Near the external urinary meatus it curved sharply downward. Straining caused slight descent but no major deformity of bladder contour.

Group 2.—Continent multiparas demonstrated considerable alteration in urethrovesical relationships. As mentioned by Muellner,[2] the bladder appeared flabby. Deficient support to the bladder base was evident from the pointed appearance.

The internal urinary meatus was located at the midbladder plane at the apex of the pointed base. The urethra was tortuous and slightly elongated. Straining caused a downward and backward rotation of the bladder in its relation with the urethra.

As a result of rotation, the internal urinary meatus was assimiliated into the anterior bladder wall. This change brought about elevation of the internal urinary meatus above the level of the most depressed portion of the bladder. The urethra described a curve with the convexity upward which was increased by straining.

Group 3.—The urethrocystographic studies performed upon patients complaining of urinary stress incontinence demonstrated consistent alteration in urethrovesical relationships.

The nonstraining films showed the pointed bladder base as described by Muellner.[2] The internal urinary meatus was located in the midplane at the apex of the pointed base.

Straining resulted in vertical descent of the bladder and urethra. Downward and backward rotation of the bladder did not occur in patients with urinary stress incontinence. Failure of rotation resulted in the internal urinary meatus plunging to the most dependent bladder level where it was subject to maximum stress. There was no evidence that the urethral length was altered by straining and the accordian effect described by Ball and associates[8] was not demonstrated.

Factors Involved in Urinary Continence.—From these studies, three factors appeared of importance in urinary continence in the female. The most important was an intact sphincter mechanism. In the nullipara the internal urinary meatus, from its dependent location, was required to support full hydrostatic pressure.

The second factor was related to hydrostatic pressure. Deficient support to the bladder floor caused vertical elongation of the bladder. This alteration in bladder configuration increased the hydrostatic pressure to be supported by the most depressed portion of the bladder. Downward and backward rotation of the bladder caused relative elevation of the level of the internal urinary meatus away from the area of maximum hydrostatic pressure. It appeared possible that a partially weakened sphincter mechanism could function adequately under such circumstances. These features possibly applied to continent multiparas with deficient bladder floor support.

In contrast, patients of Group 3 suffering from urinary stress incontinence demonstrated vertical downward thrust of the bladder and urethra with the internal urinary meatus remaining at the most depressed bladder level where it was required to resist full hydrostatic pressure.

The sphincter mechanism of these patients was constantly bombarded by the hydrostatic pressure influences of straining. The development of urinary stress incontinence in these circumstances resembled the gradual development of abdominal-wall hernia in patients with fascia weakness.

The third factor of importance was the mechanical effect produced by downward and backward rotation of the bladder on the fixed, or relatively well-supported, urethra. The stretching effect of the downward thrust of the poorly supported bladder floor would involve the sphincter mechanism less, if it were displaced to a higher position along the anterior bladder wall. Under such circumstances a "pinch" or "flutter-valve" effect at the internal urinary meatus might result.

Operative Results.—When these three factors were applied to the anatomical results of operative procedures recommended for stress incontinence, the reasons for success were seen to be entirely different. Vaginal plastic operations, such as the Kennedy procedure, strove for restoration of normal anatomy and physiology. Urethrocystographic studies demonstrated normal relationships after these operations.

With urethral suspension operations, an opposite physiological principle was involved. The Marshall-Marchetti operation stressed retropubic fixation of the anterior vaginal wall as an essential feature. Urethrocystographic studies on patients subjected to this procedure demonstrated that the operation accomplished elevation of the internal urinary meatus with pronounced backward rotation of the bladder. The postoperative result duplicated the urethrovesical relationships in straining continent patients with uterine prolapse. Because this operation did not involve repair of the vesical sphincter, it was evident that success of the operation depended upon alteration of hydrostatic pressure on the internal urinary meatus and the mechanical benefit of dislocating the internal urinary meatus to the anterior bladder wall.

From these studies, it appeared likely that failure could be expected from all types of operative procedure recommended for relief of urinary stress incontinence. A greatly relaxed, unrepaired sphincter mechanism would possibly be inadequate despite urethral suspension, in some instances. On the other hand, the sphincter mechanism may be so damaged that continence would not be restored after its extensive repair. Meigs[15] and Ball and collaborators[8] suggested that a combination of urethral suspension and plastic repair might be necessary in some patients. In practice this is the procedure commonly followed. Many advocate plastic vaginal surgery first, and if this fails, follow with one of the urethral suspension operations.

Summary and Conclusions

Through the employment of the metallic bead chain technique for urethrocystography, the relationships of the urethra and bladder were investigated. Undistorted urethral configuration was studied in relation to normal and disturbed bladder physiology.

For purposes of comparison, three groups of patients were studied. The normal group demonstrated that urinary continence was a function of adequate sphincter activity for control and release of intravesical hydrostatic pressure.

Continent multiparas with various degrees of bladder-floor relaxation demonstrated backward and downward rotation of the bladder with relative elevation of the internal urinary meatus along the anterior bladder wall. In such instance the internal urinary meatus was removed from the area of maximum hydrostatic pressure.

Patients suffering from urinary stress incontinence demonstrated downward vertical thrust of the bladder and urethra without rotation. The internal urinary meatus in patients with stress incontinence remained in the area of maximum hydrostatic pressure during the straining effort.

These studies demonstrated that the Kennedy procedure produced restoration of normal anatomy. Success of the operation depended upon proper repair of the sphincter mechanism.

The urethral suspension operations, such as the Marshall-Marchetti procedure, alter urethrovesical relationships in a fashion duplicated by patients suffering from prolapse of the uterus. Substitution of backward and downward rotation of the bladder with anterior fixation of the urethra, for vertical downward thrust of the bladder and urethra, accounted for success.

This method of study of the relationships of the urethra and bladder demonstrates several advantages. The patients were studied in the standing position. Roentgen detail was clear in both the anteroposterior and lateral positions. Undistorted urethral configuration was obtained under conditions of rest and strain. The method was easy to learn and simple in application.

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MORBIDITY AND MORTALITY IN TOTAL HYSTERECTOMY*

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THIS study consists of a survey of the morbidity and mortality in a series of hysterectomies, for patients with a preoperative diagnosis of benign pelvic disease, from the Tulane Gynecological Service of the Charity Hospital of Louisiana at New Orleans. In spite of the fact that all patients with abnormal cervices were biopsied before hysterectomy and all patients with abnormal bleeding at or past the menopause were curetted prior to operation, nine cases of incidental carcinoma were discovered at histologic examination of the specimens removed. This report includes 538 hysterectomies performed during a two-year period beginning July 1, 1950, and ending July 1, 1952. The object of this study is an attempt to show that total hysterectomy can be done safely in all instances that require removal of the uterus.

Our staff has for many years been in favor of total abdominal hysterectomy rather than supravaginal hysterectomy. However, a few were still of the opinion that supravaginal hysterectomy was the procedure of choice in some instances, and their percentage of total hysterectomies for benign disease did not nearly approximate the percentage of those who had realized that the total hysterectomy was the more desirable procedure. Each year during the past ten years on the Tulane Gynecological Service there has been a continued decrease in the number of supravaginal procedures with a concomitant drop in the mortality rate. In 1941 Miller and Prejean[1] reported 828 hysterectomies from the Tulane Service for the years 1939 and 1940 (Table I). Forty per cent of the 629 abdominal were of the supravaginal type. During the five-year period, 1946 to 1951, there were 2,097 hysterectomies on the Tulane Service at Charity Hospital. Of 1,546 abdominal procedures, 110 were supravaginal hysterectomies (7 per cent) (Table II). Of the 362 abdominal hysterectomies reported in this series in only 2 (0.5 per cent) was the cervix left in situ (Table III).

In 1950 the Chairman of the Tulane Gynecological Service established a rule that no supravaginal hysterectomies were to be done on this service. This study comprises the results of this edict which at the time of its enactment appeared to be somewhat far reaching and to our knowledge had not been attempted on a similar group of patients.

It has been argued that the decrease in morbidity and mortality observed where total hysterectomy has been performed was due to the fact that this procedure was used in the more favorable cases, while the supravaginal procedure

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was reserved for the so-called bad risk case, or patients with extensive pelvic pathology. It was only by adopting the aforementioned rule that a study could be made of the comparative value of the two procedures, utilizing the same material, staff, and facilities. Irradiation therapy and/or repeated uterine curettage for control of benign disease have not been used on the Tulane Service since January, 1946. Patients with abnormal uterine bleeding, pelvic pain, or benign tumors were treated by hysterectomy irrespective of the patients' age or physical condition. It is to be re-emphasized that in no case was the patient denied the benefit of hysterectomy because of any of these factors.

TABLE I. HYSTERECTOMY, JAN. 1, 1939, TO JAN. 1, 1940

TYPE			MORTALITY
Abdominal	629	(86.1%)	
Total	374	(59.6%)	5 (1.33%)
Supravaginal	255	(40.4%)	7 (2.75%)
Vaginal	199	(23.9%)	2 (1.00%)
Total	828	(100%)	14 (1.68%)

TABLE II. HYSTERECTOMY, JANUARY, 1946, TO JANUARY, 1951

TYPE			MORTALITY
Abdominal	1,546	(74%)	
Total	1,436	(93%)	9 (0.63%)
Supravaginal	110	(7%)	6 (5.45%)
Vaginal	551	(26%)	2 (0.36%)
Total	2,097	(100%)	17 (0.81%)

TABLE III. HYSTERECTOMY, JULY 1, 1950, TO JULY 1, 1952

TYPE			MORTALITY
Abdominal	362	(67%)	
Total	360	(99.5%)	2 (.55%)
Supravaginal	2	(0.5%)	0 (0%)
Vaginal	176	(33%)	0 (0%)
Total	538	(100%)	2 (.37%)

Our reasons for selecting the total rather than the supravaginal procedure are:

1. The frequency of return of patients with symptoms referable to the cervical stumps. The symptoms noted are leukorrhea, pelvic pain, backache, vaginal bleeding, dyspareunia, and urinary discomfort.

2. The possible development of malignancy or its presence in the cervix at the time of surgery. It has been reported that malignancy of the cervical stump after supravaginal hysterectomy has an incidence of from 2 to 8 per cent.[2] Collins[3] reported that in patients with the cervical stump who had bleeding as a symptom, 11.9 per cent had cancer of the cervix.

3. Our belief that total hysterectomy will result in a lowered morbidity and mortality.

Material

The material in this series consists of 538 hysterectomies. There were 360 total abdominal, 2 supravaginal, and 176 total vaginal (Table III). Included

in this group are 211 white and 327 Negro patients with an age distribution of from 17 to 72 years as noted in Table IV. Fifty per cent of the patients were over 40 years of age.

TABLE IV. DIVISION BY AGES, HYSTERECTOMY, JULY, 1950, TO JULY, 1952

AGE IN YEARS	NUMBER
Less than 20	2
20-30	68
30-40	201
40-50	201
50-60	42
60-70	23
70 and over	1
Total	538

Despite the request of the Chairman of the Department that no supravaginal hysterectomies be performed on the Tulane Service it was found that two operations of this type were done during this period. In the first case, that of a Negro woman, aged 34 years, with large fibroids and pelvic inflammatory disease, the cervix was left in because of so-called technical difficulties; however, this cervix was later removed vaginally at a second operation with ease. We are of the opinion that had the surgeon been a little more persistent in his efforts, a total hysterectomy could have been performed without jeopardizing the patient's life. In the second case, of a Negro girl, aged 17, with large bilateral tubovarian abscesses, the surgeon gave shock as his reason for not removing the cervix. It is interesting to note that after shock had successfully been combated, an incidental appendectomy was performed. Certainly in this case total hysterectomy could have been performed without increasing the risk to the patient.

Pathology

The pathologic conditions encountered at operation are shown in Table V. This table is compiled from the reports by the Department of Pathology on tissue removed at surgery. Of the 176 patients with pelvic inflammatory disease alone or with other benign pathology, 39 had large bilateral tubovarian abscesses. In 3 of these an abscess had spontaneously ruptured intraperitoneally prior to admission to the hospital. One of the deaths occurred in such a case.

TABLE V. PRIMARY PATHOLOGICAL DIAGNOSIS, HYSTERECTOMY, JUNE, 1950, TO JULY, 1952

	PERCENTAGE	TOTAL PERCENTAGE
Leiomyomas	25.7	
Leiomyomas, inflammatory disease	19.2	44.9
Inflammatory disease		13.1
Cervicitis	7.8	
Cervicitis, prolapse	24.3	32.1
Ovarian disease		2.5
Endometriosis, adenomyosis		1.9
Ectopic pregnancy		.7
Miscellaneous, including atypical hyperplasia, prolapse		4.8
Total		100

As previously stated, there were 9 cases of early cancer discovered on routine histologic examination of tissue removed at the time of operation (Table VI). In 5 cases, intraepithelial cancer of the cervix was discovered. This is an important finding, as biopsy of these cervices had previously failed to disclose the

malignancy. Two cases of intraepithelial cancer of the endometrium were discovered. In 2 cases, early noninvasive, well-encapsulated papillary cystadenocarcinoma of the ovary was found.

TABLE VI. CARCINOMA FOUND, HYSTERECTOMY, JULY, 1950, TO JULY, 1952

LOCATION	TYPE	NO. CASES
Cervix	Carcinoma in situ	5
Endometrium	Adenocarcinoma	2
Ovary	Papillary cystadenocarcinoma	2
Total		9 1.48%

Mortality

There were two deaths among the 538 patients. No deaths were encountered in cases in which vaginal hysterectomy was performed. In the 360 total abdominal hysterectomies performed there were 2 deaths. Neither of the 2 patients in whom supravaginal hysterectomy had been performed failed to survive. The mortality rate for the total abdominal hysterectomy series was 0.55 per cent.

If total hysterectomy had been performed in the 2 cases where the supravaginal procedure was utilized and had both these patients died as a result of this, a mortality figure of 1.10 per cent would have resulted, which is comparable to the rate encountered in the period 1946 to 1951, when only 93 per cent of the abdominal hysterectomies were of the total variety (Table VII). This comparison is controlled as the same physical facilities, anesthesia, and practically the same staff were present in both groups, as were blood banks, antibiotics, and other chemotherapeutic agents. In neither of the 2 deaths reported in this series could the procedure of total hysterectomy be held accountable for the patients' demise.

TABLE VII. MORTALITY, ABDOMINAL HYSTERECTOMY

PERIOD	TOTAL HYSTERECTOMY	MORT.	SUPRAVAGINAL HYSTERECTOMY	MORT.	ALL CASES	MORT.
Jan., 1939–Jan., 1940	374	1.33%	255	2.75%	629	1.90%
Jan., 1946–Jan., 1951	1,436	0.63%	110	5.45%	1,546	0.96%
July, 1950–July, 1952	360	0.55%	2	0.00%	362	0.55%

The first death was that of a Negro woman, aged 63 years, admitted with findings and symptoms of acute pelvic inflammation. A cul-de-sac puncture was done, followed by a colpotomy several days later. A cheesy material was obtained in both instances. On the twelfth day she was operated on and a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed because of a ruptured dermoid cyst. A diffuse peritonitis of the chemical type was present. This patient died on the thirty-third postoperative day as a result of peritonitis. No autopsy was obtained..

The second death was that of a Negro woman, aged 69, who was admitted with an acute abdominal condition and acute myocardial failure. She was operated on by the surgery department through a transverse abdominal incision at the level of the umbilicus. She was found to have degenerating fibroids and a ruptured tubovarian abscess. Members of our Gynecology staff were called and a total abdominal hysterectomy and bilateral salpingo-oophorectomy effected. She died on the third postoperative day, apparently as a result of myocardial failure. No autopsy was obtained.

Morbidity

In reporting the morbidity in this series we used the standard temperature elevation to 100.4° F. on any two successive days following the day of operation or a temperature of 102° F. on any one day following the day of surgery (Table VIII). Morbidity was found in 201 patients of the 538 operated upon, which is an incidence of 37 per cent. This compares favorably with the morbidity reported by Leventhal and Lazarus[4] of 35.04 per cent; J. H. Pratt and associates,[5] 27.2 per cent; Danforth,[6] 28.2 per cent; and Curtis, Suckow, and Huffman,[7] 40.82 per cent. Of the 360 total abdominal hysterectomies, 33.30 per cent of the patients were morbid and of the 176 vaginal hysterectomies, 45 per cent of the patients were morbid.

TABLE VIII. MORBIDITY, HYSTERECTOMY, JULY, 1950, TO JULY, 1952

AUTHOR	YEAR	TYPE*	NO. CASES	MORBIDITY PER CENT
1. Leventhal and Lazarus[4]	1951	T and V	600	35.04
2. Pratt et al.[5]	1951	T	323	27.2
3. Danforth[6]	1946	T	500	28.2
4. Curtis et al.[7]	1950	T	343	40.82
5. Authors' series	1952	T	360	33.3
		V	176	45.0

* T = Total abdominal hysterectomy.
V = Vaginal hysterectomy.

This morbidity of 37 per cent is accounted for by the following complications (Table IX). There were 85 instances of urinary retention and infection, which conforms to the usual experience of others in accounting for morbidity. The problem of preventing this common complication when the total abdominal or vaginal hysterectomy is done still remains a difficult one. There was one ureteral and one bladder injury but both occurred in the vaginal hysterectomy group. Holloway[8] reports an incidence of injury of 1.67 per cent in his series of 1,620 hysterectomies of all types. The incidence in this series is 0.37 per cent which we consider remarkably low, especially when considering the extensive pathology with which we had to deal.

Severe hemorrhage from the vaginal cuff occurred in one patient, requiring ligation of the hypogastric artery on one side. There were 2 cases of thrombophlebitis, one of which was controlled by ligation of the inferior vena cava. The other case was secondary to intravenous therapy.

Cuff abscesses and hematomas were present in 17 patients. Abdominal wound abscess and hematoma developed in 15 patients and in 3 of them eviscera-

TABLE IX. POSTOPERATIVE COMPLICATIONS, HYSTERECTOMY, JULY, 1950, TO JULY, 1952

Urinary retention and infection		85
Urinary tract injuries		2
Bladder	1	
Ureter	1	
Hemorrhage		1
Vaginal cuff	1	
Vascular		2
Vena cava ligation	1	
Cuff, abscess and hematoma		17
Wound		18
Abscess and hematoma	15	
Evisceration	3	
Pulmonary		5
Ileus and obstruction		6
Parotitis		1
None		401
Patients with physiological morbidity		74

tion took place. The remaining complications were pulmonary in 5, ileus and/or intestinal obstruction in 5, and acute parotitis in one. In 401 patients there were no postoperative complications. In this group the average postoperative stay was eight days.

All patients have been followed to date for from three months to two years in the postoperative gynecological clinic. These patients are usually discharged after eighteen months' satisfactory follow-up. There were no instances of vaginal vault prolapse or fistulas. The majority of patients can be classified as having a good result and most of them stated that they were relieved of their complaints.

Summary

1. We have reported the results of 538 consecutive unselected hysterectomies from the Tulane Gynecological Department at Charity Hospital of Louisiana at New Orleans. There were 360 total abdominal and 176 total vaginal. There were 2 supravaginal hysterectomies.

2. There were 211 white and 327 Negro patients with an age distribution of from 17 to 72 years of age, 50 per cent of whom were over 40 years of age.

3. The mortality in this series was two deaths, or 0.37 per cent.

4. The morbidity in the entire group of unselected cases was 37 per cent. The morbidity in the total abdominal group was 33.3 per cent.

5. Of the 176 patients with pelvic inflammatory disease alone or with other benign pelvic pathology, 39 had large bilateral tubovarian abscesses.

6. There were 9 cases of incidental carcinoma found, or an incidence of 1.48 per cent. Of these, 5 were intraepithelial carcinoma of the cervix.

Conclusions

This report indicates that it is possible to perform total hysterectomy in every instance that requires removal of the uterus. This is true in all cases irrespective of the pelvic pathology or severe medical complications present. The mortality and morbidity in this series compare favorably with those of all series reviewed. Since 1939 we have reduced our incidence of supravaginal hysterectomies from 40.4 per cent of the 629 abdominal cases as reported by Miller and Prejean to 0.5 per cent of the 362 abdominal cases reported in this series. A concomitant decrease in mortality is noted as the number of supravaginal procedures decreases.

We do not believe that surgery is contraindicated because of cardiac status, obesity, hypertension, kidney disease, diabetes, or other complicating conditions in the patient having symptomatic benign pelvic disease. These complicating factors, however, were adequately controlled before the patient was subjected to surgery. Therefore, this series represents a totally unselected group of patients.

We realize that the dictum we have followed for the past two years is contrary to the general teaching. However, we believe that our results, particularly as to mortality and morbidity, as given in this report, justify a continuance of this policy.

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Discussion

DR. A. F. LASH, Chicago, Ill.—The authors have demonstrated that total hysterectomy may be done safely. In 1951, Greenhill and Loeff, reporting from the Cook County Hospital, found in the period 1926 to 1930, 551 total and 1,408 supravaginal hysterectomies, while during the period 1942 to 1947, there were 1,250 total and 1,415 supravaginal hysterectomies. From Michael Reese Hospital, Stein reported in 1951 that of 561 hysterectomies, 94 per cent were total, with 60 per cent done abdominally and 40 per cent vaginally. In this group there was no operative mortality.

The trend toward total hysterectomy is generally accepted. In the last twenty years there has also been a general improvement in surgical results because of the blood banks, antibiotics, chemotherapy, better anesthetists. However, there is a lack of general appreciation among some gynecologists of proper preoperative preparation, medical evaluation of the patient's myocardial, vascular, and renal status. For we still must recognize those intangibles of operative procedures such as myocardial failure, gastric dilatation as well as ileus, and the lower nephron syndrome. Atelectasis and postoperative pneumonia have not entirely disappeared. Pulmonary embolism also stalks the convalescent although the incidence has been decreased as a result of early ambulation.

Therefore, we differ with the essayists when they say that hysterectomy may be performed irrespective of the patient's age or physical condition. In these complications we feel that we need help from our medical colleagues.

It is my opinion that the gynecologist must be the one to decide whether an abdominal total, subtotal, or vaginal hysterectomy should be performed. The condition of the patient, pathology in the pelvis, and the skill of the surgeon are the determining factors. Much as I agree with the authors on the superiority of total hysterectomy, in teaching medical students I feel obliged to demonstrate subtotal hysterectomy because most of them will become general practitioners in rural communities. I am sure the mortality and morbidity resulting from total hysterectomy performed by these occasional operators would far outweigh that resulting from the remaining cervix. At the same time, when a cervix is left behind, the responsible surgeon will keep it under observation for the rest of the patient's life or remove it vaginally later, if symptoms arise from any pathological changes. Thus it is not competition of one operation against another but rather the selection of the proper operation. We should try to fit the operation to the patient, rather than the patient to the operation.

What is most significant in their survey is the high incidence of incidental carcinoma (9 in 538); 5 intraepithelial of the cervix, 2 intraepithelial of the endometrium, and 2 early noninvasive papillary cystadenocarcinomas of the ovary. Today the answer to our cancer problem is indeed the removal of the noninvasive carcinoma or asymptomatic lesion.

In spite of the excellent results achieved by the authors, we must not forget the morbidity encountered. The complication of 3 eviscerations in 362 abdominal operations might be considered a bit high, compared to the expected incidence of 3 per 1,000 laparotomies. Surgery, although safer than formerly, is still fraught with danger, and there are occasions, as in extreme endometriosis or parametritis, when the performance of the subtotal operation may be the better part of valor. There is no victory in removing a benign cervix only to leave the patient with a urinary or fecal fistula.

DR. C. J. VOGT, Cleveland, Ohio.—I wish to present a short statistical survey of over 3,000 hysterectomies performed at the University Hospital in Cleveland.

Dr. William H. Weir, until his retirement two years ago (and now emeritus) Professor of Gynecology, School of Medicine, Western Reserve University, as early as 1910 had urged

total hysterectomy whenever possible. This teaching was based on the two premises that Dr. Johnson mentioned—first, the elimination of the possible carcinoma of the cervical stump, and, second, the eradication of possible sources of chronic vaginal discharge.

His well-known technique of total hysterectomy with the use of primary suture on all vascular pedicles is well known to all of you.

In order to compare our results with those of the New Orleans hospital group, I am using statistics that were prepared by Dr. Weir's son, Dr. William C. Weir, covering the ten-year period between 1935 and 1945. This was before most of the antibiotics except the sulfonamides, and before the liberal use of transfusion and early ambulation. It is a series in which every member of the visiting staff and house staff participated.

While our ratio of supravaginal to total hysterectomies is about 1 to 4—and for this I must apologize—I might say that two or three men who preferred supravaginal hysterectomy are now converts. Further, the less-skilled men in training were not quite willing, in some instances, to dig down that extra 2 cm. in instances of inflammatory pelvic disease.

In discussing morbidity, we used the same criteria as does Dr. Johnson. In this ten-year period, 667 supravaginal hysterectomies were performed with a morbidity of 52 per cent. The mortality rate in the supravaginal group was 1.5 per cent.

A total of 2,709 total hysterectomies were performed with a morbidity rate of 46 per cent. In this total hysterectomy group there was a postoperative mortality of 0.9 per cent.

I must say that I am happy to report that, during the last 18 months, on a busy gynecological service, we have had no mortalities.

In total hysterectomy one must consider operative accidents such as injuries to the ureter, bladder, and bowel. Injury to the ureter occurred a little over once in 300 cases. Injury to the bladder happened about 3 times in 300 cases, and injury to the bowel was slightly less than twice in 300 cases.

I must say that we at the University Hospitals of Cleveland certainly agree with Dr. Johnson that total hysterectomy is the procedure of choice. I think that the clean total hysterectomy is the gynecological procedure that separates the men from the boys, and I might say, parenthetically, separates the well-trained gynecologist from the general surgeon.

DR. HAROLD C. MACK, Detroit, Mich.—A few years ago, my associate, Roger Siddall, and I published the results of a comparative study of total versus subtotal hysterectomies, in a series of more than 6,600 operations which were performed in Harper Hospital in Detroit over a period of 18 years.

Our study showed that, in the final years of the period studied, the mortality rates of the total and subtotal operations became nearly equal, whereas in the early years the risks of the total operation far outweighed those of the supravaginal.

There were many reasons for the results, the chief ones being related to better surgical technique—not technique in the sense of cutting and sewing but in the more important matters of pre- and postoperative care, blood transfusions, attention to fluid balance, anesthesia, and better surgical judgment in the selection of operations to fit the needs of the patient. The most striking improvement was noted when blood transfusions became readily available. Chemotherapy and antibiotics seemed to play a less important part.

We have not repeated the study in the past two years, but I have little doubt that today the figures would be even more favorable. It seems to me, therefore, that since the risks of the two procedures have been equalized, the perennial debate of total versus subtotal hysterectomy is now largely a historical issue.

There is little reason to select the subtotal operation except under conditions which make the total a more hazardous procedure for the patient. I think no one can deny that, technically, the total operation is more difficult. The point I wish to emphasize is that we must not blindly follow a stubborn determination always to perform the total extirpation.

There are two dangerous words—*always* and *never*. There are times when discretion is the better part of valor, and, under difficult situations such as an advanced endometriosis, for example, it may be desirable—not cowardly—to retreat to the less difficult subtotal operation.

DR. JOHNSON (Closing).—We at Tulane, of course, are a teaching institution. However, as far as Charity Hospital is concerned, we feel that we are not necessarily teaching medical students the advisability of total over supravaginal hysterectomy. We are teaching residents, and, with our three-year resident system, we feel very strongly that no resident should leave our service without being capable of doing the total procedure under any circumstance.

I agree with the discussants concerning the occasional operator. It is quite true that his incidence of injuries to the bladder and to the bowel will be greater if he stubbornly attempts to do a total procedure. We do realize that technically it is a more difficult procedure.

At Charity Hospital the majority of our patients are Negroes and (for what reason I am not aware) endometriosis does not seem to occur as commonly as pelvic inflammatory disease. Their inflammatory diseases are notoriously gonorrheal in origin, and there are many tubovarian abscesses. Their presence makes the procedure technically somewhat difficult but certainly does not make the total operation impossible, at least in our experience.

Our biopsies are multiple biopsies. Seventy-five per cent of the surgery on our service is done by the residents, under supervision of one of our staff. The difficult cases with extensive pelvic inflammatory disease, with or without large myomas are usually handled by one of our senior staff men. The wound closures are always done by the resident. Residents are also taught to reopen any wound on the slightest suspicion of disrupture. This will tend to improve the diagnosis of disrupture, as small or partial disruptions might otherwise be missed.

COLPOCLEISIS*

KENNETH E. COX, M.D., AND ROBERT F. LAMAR, M.D., KANSAS CITY, MO.

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OUR interest in this operation stems from the multitude of problems that arise in the care of patients in a Tumor and Cancer Service. That we encountered seven cases in a short period of time in a relatively small service reflects an improvement in policy whereby every member of the staff resolved to do everything within reason to make the patient's existence as comfortable as possible.

In the 7 cases of vaginal fistulas following radiation therapy for cancer of the cervix, reported here, the two vesicovaginal fistulas had been treated elsewhere, nine and twenty-one years previously, and these patients appeared in our clinic for follow-up. Of the 5 patients with rectal fistulas, 3 had survived three years or longer, apparently cancer free. The remaining 2 had carcinoma present at the site of the fistula at the time of operation, and were considered to be in a terminal condition from the standpoint of further treatment of the cancer. Two of the patients were returned to the Tumor and Cancer Service after many years by order of the Federal Government under the Harrison Act, for morphine addiction. Separation of the patient from the drug was a part of the rehabilitation program prior to surgery. The patients were told that sufficient time had elapsed to classify them as "cured" of their original disease; and that while their extensive fistulas could not be cured by primary repair, a near 100 per cent control of feces and/or urine could be achieved by closure of the vagina.

Review of Indications in Past 100 Years

The history of the operation of colpocleisis extends over a hundred years, and the attitude of the profession as reflected in published articles shows well the effect of the teachings of the expert gynoplastic surgeons of fifty years ago and the effect of the use of radiation in the treatment of cervical cancer. It is instructive, therefore, to review the indications for colpocleisis through the past hundred years.

Simon's paper in 1855 (quoted by Kelly[1]) presented the eight indications for closure of the vagina:

1. An extensive loss of tissue, rendering it impossible to approximate the margins of the fistula.
2. Inaccessibility of fistula.
3. Destruction of the uterine cervix, bringing the peritoneum dangerously near the seat of operation.
4. Severe hemorrhage into the bladder after an operation.
5. Incarceration of the cervix uteri in the bladder.
6. Atresia of the vagina above the fistula.
7. Atresia of the urethra, with a fistula above and below it.
8. Ureterovaginal and ureterouterovaginal fistula.

*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

Fifty years later, the attitude of the profession was stated best by Kelly.[1] "The greatest advances which have been made recently can best be signalized by citing the eight indications for colpocleisis accepted by Simon, with the remark that not one of them holds good today."

These were the days in gynecological surgery when the profession received the benefits of the ingenuity and expert ability of such men as Jobert, Sims, Abbott, Kelly, Mackenrodt, Sturmdorf, and Freund. Kelly's textbook of 1909 deseribes the various methods of avoiding colpocleisis and lists seven different methods giving credit to the author of each of these ingenious surgical maneuvers whereby the vaginal mucosa may be moved about in sliding grafts, where the body of the uterus may be employed, or where the fistula may be united to the posterior vaginal wall in a partial colpocleisis. It is interesting to note that, in this same textbook, the etiology of such fistulas listed by Kelly did not include the effects of radiation. Sturmdorf, in 1919, restated Kelly's remarks regarding the use of colpocleisis[2]: "Nothing serves more to signalize gynoplastic progress during the past fifty years than the statement that not one of the indications postulated by Simon for colpocleisis with its morbid sequelae is valid at the present time. No case of vesicovaginal fistula, whatever its extent, should be considered hopeless from a reparative standpoint provided the vesical sphinctre and adjacent portions of the urethra are intact. Surgery can repair, but cannot create a sphinctre muscle."

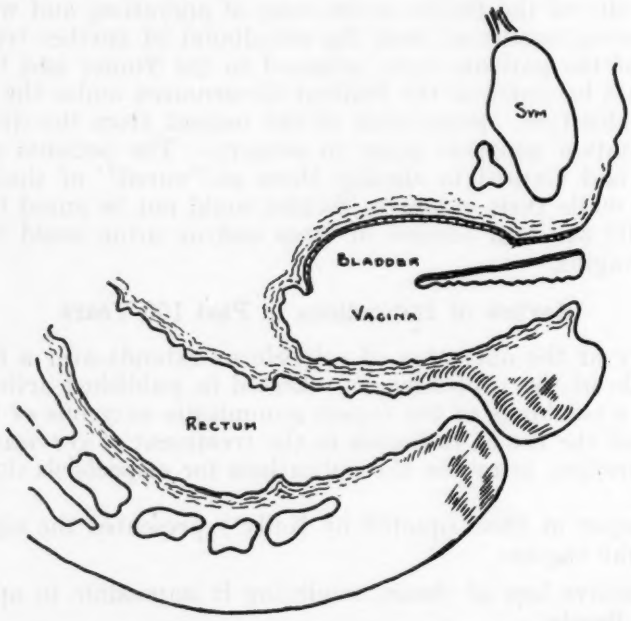

Fig. 1.—(B. H.) Extent of fistula at the time of colpocleisis. All tissue in upper two-thirds of vagina fixed, ischemic, and cartilage-like in consistency.

In these cases, where the urethral sphincter is absent, Sturmdorf recommended the operation of colpocleisis or episioclisia following the creation of a vesicovaginal-rectal fistula, and notes that the operation had been suggested as early as 1836 by Jobert, was reported several times subsequently, and was the subject of a series of 41 cases by Peterson early in this century.

In 1938, Mahfouz[3] published a monumental treatise on vesicovaginal fistula in which he stated: "In my opinion patients suffering from inoperable fistulae

should be contented with wearing a rubber reservoir rather than submit to an operation attended with such risks.'' This author further does not favor transplantation of the ureters as a very successful operation and does not discuss colpocleisis with vesicovaginal-rectal fistulas, using the rectum as a reservoir for urine.

Carter and associates[4] in 1952, in reporting a series of 73 patients with urinary-vaginal fistulas, noted that in the entire group failure in 8.8 per cent was encountered. Eleven of his cases were the result of radiation therapy and in this group failure in 41 per cent was encountered, which led Carter to conclude, ''Fistulas which occur after radiation therapy and after radiation therapy followed by some type of abdominal hysterectomy contribute the highest rate of failures. The ability to mobilize tissues adequately, without destroying the blood supply, and to close these tissues carefully and easily in layers are necessary procedures for successful repair.'' Although Carter does not mention the use of colpocleisis as a method of repair in these cases, in the discussion of his paper, Phaneuf reported his series of 43 cases with the use of colpocleisis on 2 occasions. Everett mentioned vaginal closure in 2 cases of his own. Studdiford employed partial colpocleisis 4 times in a series of 50 fistulas.

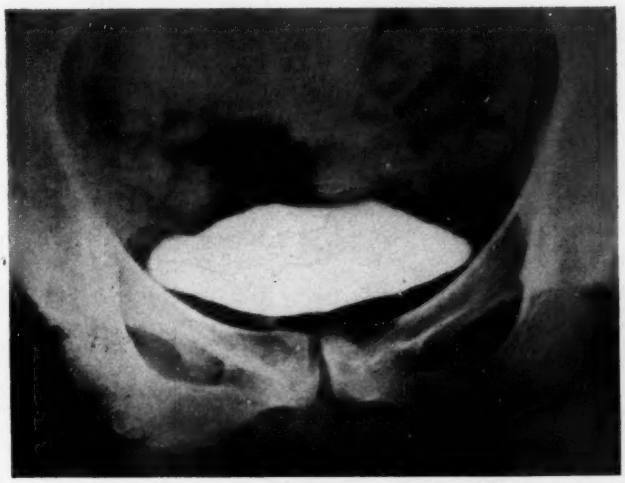

Fig. 2.—(B. H.) Anteroposterior roentgenogram of combined vagina and bladder filled with radiopaque medium showing contours almost indistinguishable from a normal bladder.

In discussing these postirradiation fistulas, Counseller[5] makes this comment, ''Although a fistula caused by treatment by radium may appear to be operable, repair is less likely to be successful than repair of fistula caused by trauma because the tissue, often for a considerable distance from the edge of the fistula, usually is too devitalized to be suitable for use in repair.'' Te Linde[6] advises, ''Those [fistulas] formed by the breaking down of carcinomatous tissue in the vesicovaginal region are usually not repairable. When the fistula is the result of a radium burn or the result of the destruction of carcinomatous tissue in the vesicovaginal septum by radium or x-ray, the closure is usually very difficult, due to reduced blood supply and excessive scar tissue.''

In our opinion, these principles apply also to extensive rectovaginal fistulas resulting from radiation therapy for carcinoma of the cervix.

Three considerations have seemed of value in the selection and management of these cases in the light of our present experience.

1. Since rehabilitation is the primary object in the management of these miserable patients, it would seem unlikely that many would submit endlessly to attempts at repair by methods that admittedly promise slightly better than an even chance of cure. More patients would be benefited if preliminary survey of the patient could promise for her a near 100 per cent cure of the fistula. In Carter's[4] series, he notes that 7 out of 11 of his patients refused additional attempts at repair after one or more unsuccessful operations.

2. In these severe cases, the vagina is at best a poorly functioning organ, due to constant contamination with urine, and/or feces, and foul exudates. In none of our series was intercourse practiced.

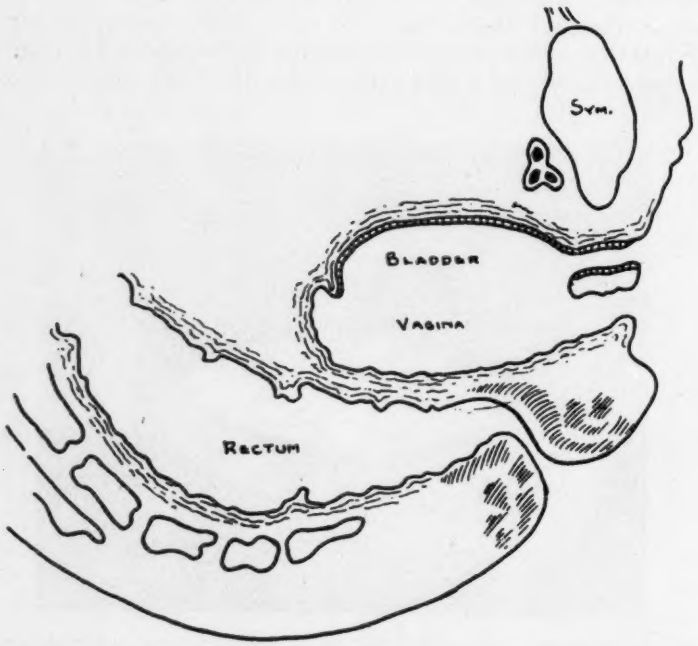

Fig. 3.—(C. S.) Extensive fistula with absence of bladder neck, vesical sphincter, and proximal urethra.

3. The operation should not be undertaken in patients whose survival time would be less than that time which would offer reasonable evidence of cure. Counseller[5] has suggested a minimum of three years. We have had five cases in which the survival, cancer free, was in excess of five years, and none in the category of less than three years' cancer-free survival (Table I). Recently, however, again in the interests of rehabilitation, we have extended the indications to include terminal cases, with no hope of cure of the cancer. Two such cases are included in this presentation (B. H., Figs. 1 and 2, and C. S., Figs. 3, 4, and 5, and Table II). We are certain that a simple procedure, easily done under saddle-block anesthesia, with negligible risk, should not be withheld from terminal cases, if it means that, with other rehabilitating measures, the patient may be easily ambulatory and less of a nursing burden, if only for a few months.

TABLE I. RECTOVAGINAL FISTULA

PATIENT	AGE (YEARS)	SURVIVAL (YEARS)	ADDITIONAL DIAGNOSES	TREATMENT	YEAR
P. L.	55	13	Morphine sulfate addiction, cured	Radium and x-ray	1939
				Colpocleisis	1948
R. H.	72	9	Tuberculous pneumonia	Radium and x-ray	1943
				Colpocleisis	1944
				Fistula repair	1944
F. H.	55	4	Residual carcinoma	Radium and x-ray	1948
			Right hydronephrosis	Colpocleisis	1950
				Colostomy	1951
B. G.	62	3	Diabetes, no carcinoma	Radium and x-ray	1948
		Died 1950		Colpocleisis	1949
A. D.	52	2	Carcinoma of bladder	Radium	1944
		Died 1951	and rectum	Hysterectomy	1950
				X-ray	1950
				Colostomy	1951
				Colpocleisis	1951

Fig. 4. Fig. 5.

Fig. 4.—(C. S.) Appearance of vulva following first urethral reconstruction. Urethral tube is of insufficient length to give satisfactory control of urine with external pressure.

Fig. 5.—(C. S.) Appearance of vulva following second plastic operation with extension of urethral tube. Control of urine for periods up to two hours with external pressure.

Technique

The technique of the operation is simple. A preliminary test is made with Allis clamps to see if the anterior and posterior walls of the vagina can be approximated without tension. A collar of vaginal mucosa is removed varying

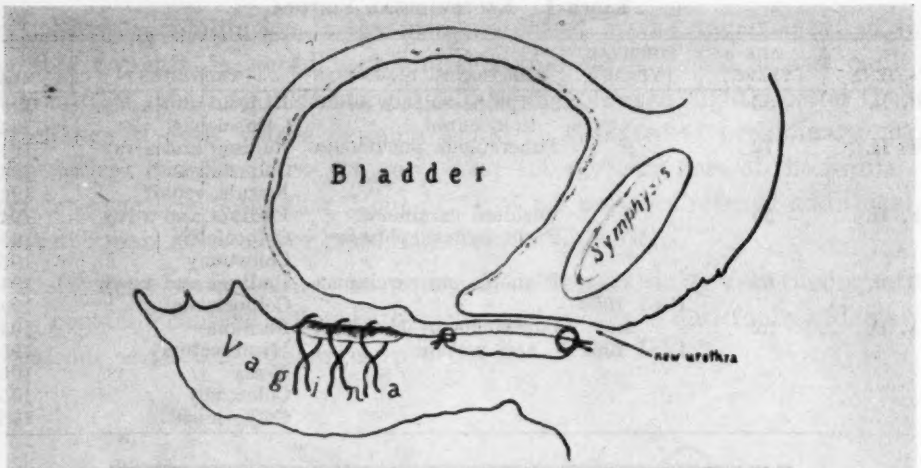

FIG. 270.—THE EFFECT OF THE OPERATION DESCRIBED IN FIG. 269 IS SEEN HERE.

The flap has been drawn forward and is united by sutures at its anterior and posterior ends to the floor of the new canal. The raw space left in the vagina is closed by a series of transverse sutures, shown in the figure still untied.

FIG. 271.—A SMITH PESSARY, WITH A HARD-RUBBER PESSARY RESTING ON TWO PILLARS, FOR THE PURPOSE OF MAKING PRESSURE ON THE NEW URETHRAL CANAL AND IN THIS WAY SUBSTITUTING THE LOSS OF THE SPHINCTER MUSCLE.

Fig. 6.—Kelly's operation, using principle of external pressure to substitute for sphincter muscle. (From Kelly, H.: Gynecology and Abdominal Surgery, W. B. Saunders Company.)

in width from 1 to 2 cm., depending on the area of normal tissue lying between the lower margin of the fistula and the hymen. If insufficient tissue is present, episioclisia is indicated. The vagina is copiously irrigated with sterile saline solution and, in rectal fistulas, is packed with narrow gauze saturated with antibiotic solution with the free end brought out into the rectum. The mucosal edge is then closed against the pack without tension with a Lembert stitch of No. 00000 catgut. The denuded submucosal tissues are then approximated in at least two layers with fine chromic catgut, and the external mucosal layer closed with interrupted fine chromic catgut. In the vaginal fistulas, a length of soft rubber tubing with large openings into the lumen at centimeter intervals is introduced through the urethra and brought out through a suprapubic cystotomy wound. This "catheter" is left in place for 18 days, and is irrigated at frequent intervals.

In Case A. D. (Figs. 6 and 7), in which the bladder neck and vesical sphincter were absent, an external urethra was made from the labia minora,

TABLE II. VESICOVAGINAL FISTULA

PATIENT	AGE (YEARS)	SURVIVAL (YEARS)	ADDITIONAL DIAGNOSES	TREATMENT	YEAR
B. H.	55	21	Morphine addiction	Vaginal hysterectomy	1931
				Radium	1932
				Fistula repair	1941
				Fistula repair	1948
				Colpocleisis	1949
C. S.	43	9	Ureterosigmoid-ostomy	Bilateral salpingo-oophorectomy	1921
				Radium and x-ray	1943
				Colpocleisis	1949
				Plastic	1950
				Plastic	1950

and later extended. Excellent control of urine was achieved by gentle continuous pressure of a small mold held in place by a perineal pad for a period of over a year. Kelly[7] has previously described somewhat similar operations (Fig. 6). In our case, however, bilateral ureterosigmoidostomy was resorted to because of severe incrustations in the resultant improvised bladder with severe ascending urinary tract infection.

Fig. 7.—(A. D.) Appearance of vagina two weeks following colpocleisis.

Conclusions

Rehabilitation of the patient must be a part of every cancer program. The end results of radiation therapy in cancer of the cervix may be less than satisfactory because of the persistence of fistulas of the urinary bladder and rectum. The success in the surgical management of these complications depends upon the nature of the fistula, the length of survival of the patient, and the presence or absence of demonstrable cancer. In attempts at repair following radiation therapy, success or failure may depend upon the ability of the operator to estimate the damage to contiguous structures by radiation and infection, resulting in their fixation, hardening, and diminished blood supply.

Colpocleisis should be considered in the management of these cases, and, in our opinion, the use of the operation should be extended to selected cases of terminal cancer, when it will be of merciful palliative value, if only for a short time.

In vaginal fistulas due to causes other than radiation treatment of carcinoma of the cervix, the admonition of Kelly, over forty years ago, as modified by Sturmdorf, still stands.

We wish to thank Miss Alma Hook for her assistance.

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Discussion

DR. JOSEPH HYDE PRATT, Rochester, Minn.—Although colpocleisis is a minor item in the armamentarium of pelvic surgery so far as the number of times that a surgeon will feel it is indicated is concerned, it is an operation which carries little risk, causing minimal disturbance to the patient, and offering good returns where indicated. There are occasions when fistulas cannot be closed in spite of repeated attempts owing to the size of the fistula or the condition of the surrounding tissues. Nowadays the chief offenders are the fistulas that follow radiation therapy to malignant lesions of the cervix or vagina, and, as has been pointed out, in these fistulas the condition of the tissues surrounding the openings is most often poor, with inadequate blood supply and marked fixation. The chance of recurrence in any one given repair is high though the great majority can be closed eventually.

In a brief review of the vaginal fistulas seen at the Mayo Clinic from 1942 through 1951, there were more than 250 cases, of which approximately six-tenths were vesicovaginal, three-tenths were rectovaginal, and a few were ureterovaginal, enterovaginal, or vesicorectovaginal fistulas. Most of the fistulas, except for the vesicorectovaginal, were repaired transvaginally, there being only 2 cases with permanent nephrostomies, 1 with ureterosigmoidostomy, and 1 with the ureter transplanted to the bladder.

The 4 cases of vesicorectovaginal fistulas were interesting. One was treated by simple repair of the rectovaginal fistula, then by bilateral ureterosigmoidostomy, since the whole base of the bladder and the trigone were missing.

The second patient was only two years post radiation for carcinoma of the cervix but had had a colostomy that was working satisfactorily. There was no evidence of recurrence of the malignant lesion and the patient was very unhappy about the urinary incontinence. Since the vesical defect was huge and closure without tension was impossible, the fundus of the atrophic uterus was pushed into the opening and the edges of the fistula were freshened and closed about the uterus. This patient was only in her forties, was married, and though a good candidate for colpocleisis, was a patient in whom we wished to preserve the vagina.

The final 2 cases are of especial interest since in both of these colpocleisis was the procedure of choice. One was thirteen years post radiation (1 abdominal exploration, 2 colostomies, 1 closure of colostomy, and 1 use of radium needles having occupied the patient's time in the interval). When seen here she was in her forties, single, had a perma-

nent colostomy functioning well and was wearing a vaginal plug to force the urine into the rectum. Colpocleisis was a very happy solution for this woman.

The final case represents the group of patients to whom we should give consideration not for cure but for palliation. This patient was one year post radiation and six months post Wertheim operation. At the latter operation positive nodes were present in both obturator fossas and one iliac chain. There was also radiation necrosis and ulceration of the terminal ileum and of the sigmoid. Therefore, resection of ileum and sigmoid with primary end-to-end anastomoses was done at the time of the Wertheim operation. Within six weeks both a vesicovaginal and a rectovaginal fistula had developed. Six months later, since intercourse was not being practiced, a colpocleisis was done, and the patient was home in two weeks with complete control of urine and feces though there is some passage of gas through the urethra. This time interval would be entirely too short for any extensive operation, considering the likelihood of recurrence with the positive nodes present but the patient has been rehabilitated to a more useful life and needs little nursing care.

EFFECT OF STILBESTROL ON PREGNANCY COMPARED TO THE EFFECT OF A PLACEBO*

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A COMPARISON will be made between a widely used dosage schedule of diethylstilbestrol and a placebo in their effect on pregnancy. Evidence will be presented that stilbestrol in these doses has an effect that is extraordinarily similar to that of the placebo.

This study was begun primarily because of the hope that stilbestrol would moderate pre-eclampsia. This was offered by the reports of Smith and Smith[1, 2, 3] from the Boston Lying-in Hospital. Pre-eclampsia, particularly that superimposed upon chronic hypertensive disease, is a tremendous problem at the Charity Hospital of Louisiana at New Orleans. Prematurity is no less a problem and hope has been offered for this also.

The basis for the use of stilbestrol in pregnancy was the evidence that it increased the progesterone-producing qualities of the placenta in women and laboratory animals. The argument has been presented that there exists a decline in estrogen and progesterone production that coincides with the appearance of pre-eclampsia, premature delivery, and other abnormalities of pregnancy; the administration of stilbestrol in progressive doses is supposed to reverse this unnatural trend. The controls used to match stilbestrol-treated patients have been inadequate. This shortcoming has been rectified here.

Method

Patients attending antepartum clinics of the Tulane Service at the Charity Hospital of Louisiana at New Orleans were given 25 mg. tablets of stilbestrol or placebo tablets. The tablets were similar in appearance except that the stilbestrol tablets were white and the placebo tablets were colored slightly yellow. When necessary each tablet could be broken into 4 equal pieces to make the prescribed daily dose. The stilbestrol tablets were known as "white stilbestrol" and the placebo tablets as "yellow stilbestrol." Only I possessed the information that the "yellow stilbestrol" tablets contained inert substances.

The tablets were dispensed at the antepartum clinics by one or wo women clerks who sat at desks apart from the regular clinic personnel. At the first visit a good deal of time was spent with each patient in order to become acquainted with her. It was emphasized that the regular taking of the tablets would help the patient and her expected baby. At each visit exactly enough tablets to last until the next clinic visit were dispensed in containers. The daily doses were carefully explained and written instructions provided.

*Presented at the Twentieth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Memphis, Tenn., Oct. 30 to Nov. 1, 1952.

An attempt was made to have an equal number of placebo patients and stilbestrol patients. The patients were alternatingly assigned to the placebo and stilbestrol groups by the clerks, who kept the primigravidas and multigravidas in separate series. No selection was exercised. An attempt was made to have as many primigravidas as possible by accepting in some weeks only primigravidas. The number of women who completed the course of placebos, aborted, or delivered while taking it is 203. The stilbestrol group contains 190 women, 13 less than the placebo group. If stilbestrol in the prescribed dosage schedule can produce a clear-cut effect on pregnancy these are enough patients to prove it.

Treatment in all cases was started by at least the twentieth week of pregnancy. The dosage scale was similar to that used by Smith and Smith (Table I). Every two or three weeks the daily dose of stilbestrol, or an equal number of segments of placebo tablets, was increased. The initial dose ranged from 6.3 mg. a day to 50 mg. a day, depending on the week of gestation the treatment was started. The last week of medication was the thirty-fifth week of pregnancy when the patient received 137.5 mg. a day.

TABLE I. STILBESTROL DOSAGE SCHEDULE

WEEKS		WEEKS	
10 and before	6.3 mg.	23	62.5 mg.
11	6.3	24	62.5
12	12.5	25	75
13	12.5	26	75
14	25	27	87.5
15	25	28	87.5
16	37.5	29	100
17	37.5	30	100
18	37.5	31	112.5
19	50	32	112.5
20	50	33	125
21	50	34	125
22	62.5	35	137.5

At the antepartum clinics and during hospitalization the placebo and stilbestrol patients were handled alike. In fact, both groups were managed exactly as were Charity Hospital patients not participating in the study except that special observations were made on the placentas when possible. This clinical experiment was started in October, 1950, and the last patient delivered in May, 1952. At the conclusion of the experiment all of the pertinent data were impartially transferred by me from the hospital records to punch cards.

Scatter.—The random grouping of this many patients as placebo patients and stilbestrol patients furnished for each group patients that were similar in all aspects with no differences in the groups that would impugn fairness in comparing them. The past obstetric history of the multigravidas did not show a preponderance of handicapped women in either group. There were five placebo women and seven stilbestrol women who had had stillborn infants. There were two women in each group who had had more than two abortions. The medical and surgical background of the women in each group was not disparate. Of the patients who had a medical or surgical disease in the past that had to be given thought during the pregnancy we are considering, there were 19 placebo patients and 22 stilbestrol patients. All cases of syphilis were adequately treated. Twenty-nine of the placebo patients were white women and 28 of the stilbestrol patients were of that race. Primigravidas viewed separately had 8 and 11 white women in each series. Considered by age there was no significant difference in the age groups of placebo and stilbestrol patients (Table II).

TABLE II. AGES OF PATIENTS

AGES (YEARS)	ALL PATIENTS		PRIMIGRAVIDAS	
	PLACEBO	STILBESTROL	PLACEBO	STILBESTROL
40 and over	2	2	1	1
30-39	40	26	4	4
20-29	102	96	37	36
10-19	54	53	50	45

The two groups were alike when compared by the week of gestation in which patients began the two regimens (Table III). There was one twin pregnancy in each group. The number of placebo and stilbestrol primigravidas, 86 and 92, were 47 per cent and 46 per cent of the total number of patients in each group. Distributed by number of pregnancies, the patients were not disproportionately scattered.

TABLE III. WEEK OF PREGNANCY TREATMENT BEGAN

WEEKS	ALL PATIENTS		PRIMIGRAVIDAS	
	PLACEBO	STILBESTROL	PLACEBO	STILBESTROL
<11	14	7	10	4
11-15	82	61	37	33
16-20	102	116	45	49

The 268 women who started in the study but did not finish had to be dropped for various reasons. Collected by reasons for dropping out, the number in each group was similar for placebo and stilbestrol patients. To illustrate why women were dropped the following data on stilbestrol women are given: 46 found it impossible to attend antepartum clinics regularly, 35 disappeared, 41 would not cooperate, and 33 provided inadequate data, for example, parts of records were lost, or the patients delivered at home. Other reasons were abortions and toxic reactions.

Results

Excluding abortions, there were 198 placebo patients and 184 stilbestrol patients who completed the dosage schedule or delivered while on it. There were no maternal deaths and no cases of eclampsia.

Pre-eclampsia.—The diagnosis of pre-eclampsia in this study is based on the development of hypertension (140 systolic, 90 diastolic) and/or proteinuria after the twenty-fourth week of pregnancy. Hypertension has to be present on at least two occasions 24 or more hours apart. Proteinuria is established by any one of the common tests, performed on a catheter specimen of urine devoid of pus or blood. There are 20 (10.1 per cent) placebo patients and 19 (10.3 per cent) stilbestrol patients with pre-eclampsia. When the primigravidas are considered separately there are more stilbestrol patients with pre-eclampsia, 14 compared to 10, but this is not a significant difference. Significance will be claimed, or rather, disclaimed, in this report only when the figures have been tested for significance by chi square.

The patients who exhibited hypertension at least once but do not qualify as having pre-eclampsia are compared as to number of patients, level of the hypertension, and week of appearance of the hypertension. They are strikingly parallel. This attempts to compare the patients for those who prefer that blood pressure elevations be only 6 hours apart to diagnose pre-eclampsia.

An effort was made to divide the cases of pre-eclampsia into severe and mild pre-eclampsia despite dissatisfaction with the term "mild pre-eclampsia." Patients with severe pre-eclampsia were recognized by two different criteria.

One criterion was systolic blood pressure of 160 or over or diastolic pressure of 110 or over. The other criterion was the total clinical impression of the seriousness of the patient's condition. This is arrived at from consideration of the blood pressure, proteinuria, edema, and the sensorium. In this type of patient it is our practice to utilize an indwelling catheter. Thus the catheter serves as a means of selecting cases of severe pre-eclampsia. By neither criterion did stilbestrol assuage pre-eclampsia. For example, among the primigravidas there were 4 placebo women and 4 stilbestrol women with severe pre-eclampsia when the general clinical appearance was used. By the blood pressure classification there were 3 women in each group. There was a difference of only 1 patient when all patients, primigravidas and multigravidas, were assembled and compared.

Furthermore, when the blood pressures of pre-eclamptic patients are broken up into groups of five levels of hypertension and compared, there is no difference. There is no dissimilarity by week of pregnancy in which the blood pressure was highest. The placebo pre-eclamptic patients and the stilbestrol pre-eclamptics are not statistically different as to the week of pregnancy in which they develop this complication.

Chronic Hypertensive Disease With Superimposed Pre-eclampsia.—I was particularly interested in the possibility that stilbestrol might prevent patients with chronic hypertensive disease from acquiring pre-eclampsia because here would be a practical use for the prescribing of stilbestrol as a prophylactic. More successful management of pregnant women with chronic hypertensive disease is one of our greatest needs at the Charity Hospital. The definitions of chronic hypertensive disease, and that disease with superimposed pre-eclampsia, used in this project, are the same adopted by the American Committee on Maternal Welfare in April, 1952. Chronic hypertensive disease is defined as blood pressure of 140 or over, systolic, or 90 or over, diastolic, appearing before the twenty-fourth week of pregnancy and persisting indefinitely after delivery. The superimposition of pre-eclampsia is defined as are elevation of systolic pressure of 30 mm. Hg or more and/or an elevation in diastolic pressure of at least 15 mm. Hg and/or the development of proteinuria.

In this study there were 28 placebo patients with chronic hypertensive disease and 11 (39.2 per cent) developed pre-eclampsia. There were 34 stilbestrol patients and 18 (52.9 per cent) had pre-eclampsia. Although there was a greater percentage of stilbestrol patients who developed pre-eclampsia this difference is not significant when tested by chi square. Unfortunately, there was also no significant difference in the week in which these patients acquired pre-eclampsia.

It should be explained why there are so many patients with chronic hypertensive disease in each series. First, we consistently have a remarkably high incidence of chronic hypertensive disease in our Negro patients at the Charity Hospital. Second, these women are a very dependable class of patients who begin antepartum care early and are faithful to their return appointments. This we think is owing to the extra attention they receive. Once started on a therapy such as this they are much less likely to drop out than other patients.

Weight Gain and Edema.—There is no significant difference in the weight gain of placebo and stilbestrol patients. This is also true when primigravidas or pre-eclamptic patients are considered separately, or when women who bore premature infants are excluded. A patient who at any time had an observer rate her as exhibiting "2 plus" edema or more is classified as having edema. There were 28 placebo patients and 27 stilbestrol patients who had this sign of toxemia. Primigravidas, viewed separately, have 14 in each treatment group.

Prematurity.—Stilbestrol has been proposed as an agent to prevent prematurity. This it has been said to accomplish by lengthening the duration of pregnancy and increasing fetal size and maturity.

Duration of Pregnancy.—The average duration of pregnancy in this study was greater among the placebo patients than the stilbestrol patients, 38.1 weeks compared to 36.6 weeks. The average was also longer in the placebo group when the primigravidas are examined separately (38.2 weeks and 37.8 weeks). These differences in average length of pregnancy are not significant. Cases in which labor was induced (6) or cesarean section performed without preceding labor (5) were omitted from these observations.

Stilbestrol offered no protection against prematurity. Designating all infants of 2,500 grams or less as prematures, there were 26 placebo prematures and 35 stilbestrol prematures. When primigravidas are viewed separately there were 16 placebo and 23 stilbestrol prematures. The prevalence of prematurity in stilbestrol-treated patients is even greater when, among primigravidas taken separately, 2,300 grams instead of 2,500 grams is used as the upper limit of prematurity in the Negro babies. Here there were only 9 prematures among the placebo infants and 17 in the stilbestrol group. The difference is found to be probably not significant when tested by chi square.

To test the proposition that infants born before the thirty-eighth week of gestation fare better if the mother had been on this schedule of mounting stilbestrol doses, all babies born before the thirty-eighth week of gestation were compared by weights. The average birth weight of all the placebo-nourished babies was greater, 2,787 grams, compared to 2,542 grams for the babies of mothers who took stilbestrol. This is not a significant difference. Among primigravidas the placebo babies also had an insignificant advantage, an average weight of 2,598 grams compared to 2,435 grams. To test this further the babies born before the thirty-eighth week of pregnancy were distributed into five separate groups by gestational age and the weights compared. There was no significant difference in weight in any group (Table IV). The survival rates among babies born before 38 weeks were not significantly different.

TABLE IV. AVERAGE FETAL WEIGHT FOR BABIES BORN PRIOR TO THE THIRTY-EIGHTH WEEK OF GESTATION, ALL PATIENTS

	PLACEBO			STILBESTROL		
WEEK OF DELIVERY	NUMBER	AVERAGE WEIGHT (GRAMS)	PER CENT IN GROUP	NUMBER	AVERAGE WEIGHT (GRAMS)	PER CENT IN GROUP
<28	2	845	4.1	2	765	4.8
30-31	4	2 273	8.2	4	1,651	6.5
32-33	5	2,539	10.2	9	1,911	14.5
34-35	12	2,778	24.5	11	2,829	17.7
36-37	26	3,122	53.0	35	2,870	56.5
Total	49	2,787	100.0	62	2,542	100.0

Regardless of the direction from which the subject of birth weight was approached, stilbestrol babies did not seem to be any better than placebo babies. The average birth weight of all the babies born to mothers who had taken the placebo was 3,080 grams and that of the babies of stilbestrol-treated mothers was 2,997 grams. Taking the primigravidas separately, the average birth weight of the placebo babies was 2,570 grams and of the stilbestrol babies, 2,805 grams. These differences are not important statistically or practically. Finally, all babies who weighed 2,500 grams or less at birth were compared to see if the

stilbestrol prematures weighed more. The average weight of the placebo prematures was 2,054 grams and of the stilbestrol prematures, 1,954 grams.

Unfortunately, the lengths of the infants cannot be compared because they were found to be inadequately recorded in the nursery.

Stillbirths and Neonatal Deaths.—The stillbirth and neonatal death records for placebo and stilbestrol patients were essentially the same. There were 4 stillbirths among placebo patients and 3 among the stilbestrol patients. The important data on these cases are:

Placebo patients:

1. Chronic hypertensive disease and abruptio.
2. Premature infant, 34 weeks' gestation, cause of death undetermined.
3. Pre-eclampsia, 31 weeks' gestation, 1,475 grams.
4. Previable infant, 23 weeks' gestation.

Stilbestrol patients:

1. Chronic hypertensive disease and pre-eclampsia, 33 weeks' gestation, 1,925 grams.
2. Chronic hypertensive disease, 30 weeks' gestation.
3. Previable infant, 21 weeks' gestation, 600 grams.

The placebo neonatal deaths number 7 and the stilbestrol deaths, 4. The relevant clinical data with survival time are summarized here:

Placebo patients:

1. Birth injury, cerebral hemorrhage, 20 minutes.
2. Premature, 21 weeks' gestation, 400 grams, 5 hours.
3. Premature, 27 weeks' gestation, 1,290 grams, 13 hours.
4. Septic, premature, 34 weeks' gestation, 1,390 grams, 36 hours.
5. Prolonged labor, disproportion, 20 minutes.
6. Septic, premature, 37 weeks' gestation, 2,380 grams, 22 hours.
7. Birth injury (?), 28 hours.

Stilbestrol patients:

1. Premature, 32 weeks' gestation, 1,420 grams, 15 hours.
2. Premature, 32 weeks' gestation, 1,225 grams, cerebral hemorrhage, 12 hours.
3. Previable, 23 weeks' gestation, 1 hour.
4. Diabetic mother, 9 days.

Abnormal Fetus.—Examination of the number and nature of major abnormalities of the fetus shows no conclusive differences in the two groups. There is 1 in the stilbestrol group, a meningocele and 5 in the placebo, namely, a meningocele, large inguinal hernia, undescended testes, an albino, and erythroblastosis.

Uterine Bleeding.—When stilbestrol is prescribed one is always interested in learning if there is uterine bleeding. There were 2 cases of abruptio placentae in each group. The one case of placenta previa appeared in a placebo patient. There were patients in each group admitted to the hospital for bleeding, the cause of which could not be determined. There was a preponderance in the placebo group, 17, as compared to 9.

The fear has been expressed that stilbestrol might cause excessive bleeding in the postpartum period. This is unjustified as abnormal bleeding between delivery and a six weeks post partum visit was experienced by 10 placebo patients and 4 stilbestrol patients. There was no remarkable number or type of postpartum complications in either group.

Other Complications.—All of the complications of pregnancy that occurred in these patients were collected and compared. They were essentially alike. If threatened premature labor is described as admission in apparent labor before 37 weeks of gestation and cessation of that labor with subsequent discharge from the hospital, this complication occurred 9 times in each of the two groups.

Toxic Reactions.—The experience with toxic reaction to stilbestrol is an interesting psychological study. Seven women had to stop taking stilbestrol because it caused nausea and vomiting. Six had to discontinue the placebo because they claimed the same reaction.

Placentas.—Working with the placentas provided by the Smith and Smith experiment, Sturgis and his associates[4] found that stilbestrol treatment produced a larger, heavier placenta. I did not find this to be so. An attempt was made to have as many placental weights and volumes recorded as possible. Request was also made to have abnormalities of the placenta recorded. The cord and membranes were trimmed off, clots wiped away, and the placenta weighed as soon after delivery as possible. The placental volume was measured by water displacement. At the termination of the experiment the specific gravity of the placentas was calculated. The number of placentas on which these observations were made were: weight, placebo 82, stilbestrol 57; volume: placebo 93, stilbestrol 56. There was no chance recognized for selection of placentas on which these special observations were to be made. When activity was light enough on the unit that provides facilities for more deliveries than any other in the United States, then the placentas were weighed and volumes determined.

The average placental weight of the placebo patients was more than for the stilbestrol patients, 466 grams to 460 grams. Those of primigravidas, separately, were 445 grams and 414 grams. The average placental volume of the placebo patients was 442 c.c. and of the stilbestrol patients, 437 c.c. Obviously, there is no need to test these figures for significance. They were equal.

The specific gravity of the placentas was determined and as would be expected they were extraordinarily alike, the means being 1.106 (placebos) and 1.110 (stilbestrol) and the medians 1.09 and 1.10. The variability in the 2 groups was also similar, 0.39 and 0.41.

Because of the placenta-stunting reputation of toxemia, the placental weights in patients with any of the hypertensive syndromes were compared separately as were those in patients who had no hypertension and there was no significant difference. The same was true with placentas of women pregnant for the first time when viewed apart from the others.

The observation as to whether or not infarcts were present in the placenta was made in 62 placebo cases and 52 stilbestrol cases. There were infarcts in 18 placebo cases and 15 in the other group.

Sturgis' group was struck by the surprising number of circummarginate placentas found in stilbestrol patients and attributed this placental overgrowth to the stilbestrol. In all of our patients there was only one who had a placenta in the overgrowth category. It was a circumvallate placenta and it occurred in a placebo patient.

Abortions.—This experiment was not designed to evaluate the effect of stilbestrol on the complications of early pregnancy but interest in the number of abortions that occurred is inevitable. Fourteen women began the placebo before the eleventh week of pregnancy and 82 in the following 5 weeks. Seven women began stilbestrol before the eleventh week and 61 in the following 5 weeks. Disregarding women who aborted or began to abort in the first week of treatment, there were 4 placebo patients and 6 stilbestrol patients who aborted.

Withdrawal of Stilbestrol.—During this experiment a question has been put to me several times. If I treat a woman successfully for threatened abortion with stilbestrol can I stop the medication with safety or will withdrawal cause either bleeding or premature labor? There were 23 placebo patients and 36 stilbestrol patients who took the tablets for ten or more weeks and then stopped for various

reasons. The average duration of gestation in each group was exactly the same, 38 weeks. One abortion followed cessation of therapy in each group. Otherwise the number of stilbestrol patients who got into difficulties outnumbers the placebo patients, 7 stilbestrol patients and 1 placebo patient, but none of the difficulties proved to be insurmountable. Each case ended with a live baby. Specifically, these complications following stilbestrol withdrawal were threatened abortion or threatened premature labor in 4 cases, bleeding of undetermined origin in 2 cases, and one premature baby at 35 weeks.

The duration of pregnancy among the patients who discontinued placebos or stilbestrol after 5 or more complete weeks of treatment was, respectively, 38.2 and 37.9 weeks.

Comment

"Did the patients take the tablets as directed?" is a question you certainly have a right to ask. I have no incontrovertible proof that they took the medicine. The clerks who dispensed the tablets discussed personal problems in an interested, unhurried way with the patients and got to know them fairly well. It was the emphatically asserted opinion of these clerks that the patients were taking the tablets as advised. More important, the plan of the antepartum clinic was such that the patient had to want to take the medicine to continue in the study. After concluding the visit with the doctor she had to seek the clerk's desk to obtain the tablets. To illustrate that the contrary course was possible, I find that 33 placebo patients and 41 stilbestrol patients were dropped from the study because they were not interested enough in the treatment to go to the clerk and obtain the tablets at every visit. As the patients participating in the study had to begin antepartum care by the twentieth week of pregnancy and return to the clinic for each scheduled visit they were an elite group of patients differing from the usual Charity Hospital patient who is likely to begin antepartum care late and attend sporadically. The patient with a conscientious and enlightened attitude toward attendance at the antepartum clinic is the type of patient likely to take her medicine as directed.

Diabetes.—The results of this experiment should interest those who are deliberating the treatment of diabetes in pregnancy with stilbestrol or stilbestrol and progesterone. Here, only one patient had diabetes and by chance she was a stilbestrol patient. Her pregnancy, except for mild chronic hypertensive disease, was successful until her baby died at home of undetermined causes on the ninth neonatal day. The help that stilbestrol offers to the diabetic mother is based on the same premises as those on which stilbestrol has been offered to other women; stilbestrol is reputed to aid diabetics by altering unfavorable hormonal levels. The endocrine imbalance is described as being the same in diabetes and in pre-eclampsia. As stilbestrol did not affect pre-eclampsia in this study the help that it would give in diabetes can be questioned. I do not propose that this study does more than raise a doubt about the value of stilbestrol in diabetic mothers.

Controls.—Much of the work with stilbestrol can be challenged because of the poverty of controls. This delays the establishment of the true place of stilbestrol therapy in women. There probably is some clinical evaluation of stilbestrol in which that drug has been compared to a placebo but I have been unable to find it. There seems to be a great reluctance to match stilbestrol against the sugar pill. Adequate controls are necessary to evaluate critically a drug. The number of controls should at least equal the number of patients treated with the medicine when clinically feasible. Placebos, undistinguishable to the patients and physicians, are the controls par excellence. In 19 reports

found at random in the library discussing the successful use of stilbestrol for various female maladies, 12 did not mention controls. In only 2 papers were there controls in numbers that equaled or exceeded the treatment group.

Contemporary patients are not completely satisfactory as controls. Contemporary patients are likely to be indifferent, less intelligent castoffs who would not cooperate or patients who began antepartum care late. It is obviously unfair to compare the obstetric performances of these patients to those of a special treatment group. It is impossible to give the same obstetric care to women treated with a special medicine as you give to patients who do not receive that medicine. The special group will inevitably receive more careful thought, more time, more sympathy and, unconsciously, decisions on management may be swayed. For like reasons, the results of pregnancy in the treated group cannot be compared to the experiences of the same women in previous pregnancies. Comparisons with statistics in other hospitals and between private and ward patients are even less valid.

Summary

One hundred ninety pregnant women received increasing doses of stilbestrol. Treatment was begun by at least the twentieth week of pregnancy and continued through the thirty-fifth week of pregnancy, unless the patient delivered or aborted while on the treatment. The dose of stilbestrol began with 6.3 mg. to 50 mg. a day and ended with 137.5 mg. a day. Two hundred three similar women received an indistinguishable placebo and provided a fair comparison. The stilbestrol had no effect on pre-eclampsia, prematurity, fetal weight and survival, or the size of the placenta. The importance of adequate controls is discussed.

Grateful acknowledgment is made of the assistance of Huldah Bancroft, Ph.D., Professor of Biostatistics, Tulane University, who helped in the design of the experiment and in the interpretation of the data evolved. Dr. James W. Hendrick also helped in the planning.

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Discussion

DR. R. R. GREENE, Chicago, Ill.—Dr. Ferguson has demonstrated clearly and unequivocally that stilbestrol does not have the miraculous or even the beneficial results claimed for it, when administered to the normally pregnant woman. More specifically, he has shown in his patients that it does not decrease the incidence of toxemia or of premature delivery. Furthermore, it does not cause babies born of treated mothers to be larger, healthier, or happier. While not mentioned by him, it apparently does not even prevent postmaturity, as was noted by another group of workers. He has very correctly stressed the absolute necessity for the use of adequate controls in an evaluation such as this; more specifically, for the use of placebo-treated controls—controls that are seen as often, have as much special attention, and tend to cooperate just as much as those receiving the stilbestrol. It is extremely unfortunate that in most of the other studies on the use of stilbestrol, for this and for many of its other purposes, no such adequate controls were included. If they had been used, there would probably be less glowing claims for stilbestrol as a universal panacea.

The difference between Dr. Ferguson's results and those originally reported by the Smiths is largely explained by his use of proper and adequate controls. There are other

explanations, however. In the first place, while the Smiths are quoted as claiming that the babies from stilbestrol-treated mothers are larger, they actually claim no such thing. What they proved to their own satisfaction was that in the stilbestrol group a significantly larger number weighed over 8 pounds than in the control group. In calculating these data, however, they used only 311 full-term babies from stilbestrol-treated mothers and 369 control babies. For some inexplicable reason they did not include the data on 45 full-term babies born of stilbestrol mothers and 123 others born of control mothers. Certainly, these data must have been available since these babies were delivered in one of the finest maternity hospitals in the United States; and I am sure they were weighed at birth. The significance of their conclusions, therefore, is vitiated by the use of only partial data.

If time permitted, there are several other points in the Smiths' presentation, both as to adequacy of data and as to logic, that might be criticized. All this is, however, not particularly pertinent. Dr. Ferguson has, I believe, driven a very large nail into the coffin that we will use some day to bury some of the extremely outsized claims for the beneficial effects of stilbestrol.

DR. C. J. VOGT, Cleveland, Ohio.—Were any excretion studies done, and if they were, was any difference in the excretion rates of the steroids found in either group?

DR. FERGUSON.—There were no excretion studies.

DR. CECIL E. WARDE, Memphis, Tenn.—It has been said that stilbestrol causes retention of dead fetuses.

DR. FERGUSON.—There were no cases of retention of a dead fetus in either the control or the stilbestrol group.

TREATMENT OF THE UNDEVELOPED SECRETORY PHASE OF THE ENDOMETRIUM*

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THE endometrium is a sensitive indicator of ovarian function, both qualitatively and quantitatively. Estrogenic activity causes progressive development from the postmenstrual through the proliferative phases. The first effects of progesterone may usually be recognized during the third week of a 28 day cycle. Sturgis and Meigs[1] and others[2, 3] describe the appearance of subnuclear vacuolization at this time, the first evidence in the endometrium that the secretory phase has begun. Progesterone inhibits further cell proliferation, and stimulates the glands toward active secretion.

In discussing the evidence for ovulation, Pommerenke[4] states that the cytologic qualities of the endometrium reflect to a high degree the condition of the follicular system. Gynecologists[3, 5, 6] generally agree that when a biopsy of the endometrium shows a secretory pattern, it offers, with very few exceptions, a satisfactory guide that ovulation has taken place. Rossman and Bartelmez[7] showed that this is also true among macaques. When ovulation was delayed in their group of animals, it was due to a prolonged period of ovarian inactivity. As expected in this circumstance, development of the secretory endometrium was also delayed until lutein function began.

The maturity of secretory pattern development was correlated with the adequacy of corpus luteum function by Heller, Farney, Morgan, and Meyers.[8] From an intensive study of 28 women subjected to pelvic surgery, they concluded that the best single measure to determine the histologic state of the ovaries is the endometrial biopsy. Considerable reliability may be placed, therefore, in this simple clinical procedure for evaluating progesterone secretion.

The timing of the endometrial biopsy is a subject which bristles with disagreement. It is granted that when these biopsies are taken three or four days before the onset of menstruation, the tissues sparkle with clarity. Neither blood, nor desquamation, nor degeneration of cells is present to confuse the diagnosis. On the other hand, a biopsy taken shortly after the onset of menstruation also has some advantages. Frequently patients in whom such studies are important have irregular cycles. Only at the menstrual time can it be stated that their maximal secretory development has been achieved. Again, when a series of biopsies are compared in order to learn the response to treatment, it is advantageous to have taken them at similar times in the cycle. Finally, the interruption of a much desired pregnancy remains a real possibility. To use contraceptives in order to permit biopsies during several cycles

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is often impractical and psychologically undesirable. After all, the ideal response to any treatment of sterility patients is the achievement of pregnancy. We are convinced that the extent of secretory development can be accurately determined from the endometrium of early menstruation, and our biopsies were usually taken at this time.

After studying many thousands of endometria, Hertig[9] concluded that the postovulatory effects are regular and progressive. These begin as early as the second day after ovulation. He described vividly the development of the secretory patterns from this time to the onset of menstruation. Moreover, he was able to set forth criteria for dating the endometria in relation to the cycle. This, then, is additional evidence that the endometrium may be used to assay quantitatively progesterone secretions.

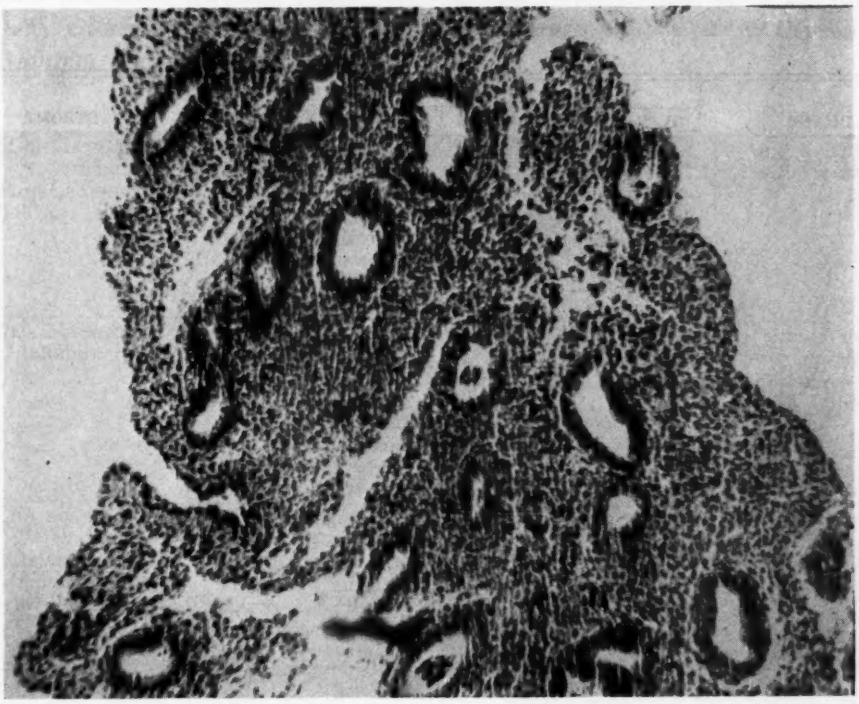

Fig. 1.—Proliferative endometrium.

During his investigations of the human corpus luteum, Brewer[10] noted that its peak of activity occurred at about the twenty-second day of a 28 day cycle. This was reflected in the endometrium by a typical pattern of marked glandular secretion and edema of the stroma. The absence of this nature development may be ascribed to either:

1. An improperly functioning corpus luteum, or
2. An endometrium which is incapable of a proper progestational response.

Of these two possibilities, the first, malfunction of the corpus luteum, is believed to be far more common than the second. A completely refractory endometrium is most unusual.

The present study was undertaken in order to answer three principal questions:

1. Without performing blood progesterone determinations, are there any clinical means, other than the endometrial biopsy, by which deficient function of the corpus luteum can be detected?

2. What can be expected of the infertile woman in whom the endometrium progresses only to the early secretory phase?

3. What improvement in corpus luteum function can be attained with the various recommended treatments?

In order to secure uniform interpretation of our biopsies, they were all submitted to Dr. A. B. Cairns for examination. He has classified these endometria into three groups with the brief descriptions given in Table I.

TABLE I

PHASE	GLANDS		STROMA
	OVER-ALL APPEARANCE	CELL APPEARANCE	
Proliferative (no secretory activity) Fig. 1	1. Active proliferation of glands and stroma 2. Glands are tubular in shape	1. Epithelium is cuboidal to low columnar. Nucleus near center of cell 2. Crowding of epithelium on basement membrane 3. No secretory activity	1. Hyperplastic and abundant 2. Numerous mitoses 3. Nuclei crowded
Early secretory (ovulation, poor lutein function). (Mixed.) Fig. 2, left	1. Glands show early convolutions with elongation of cells	1. Epithelium becoming columnar and regular with nucleus going to base of cell 2. Basilar vacuoles in early part 3. Early secretory activity	1. Hyperemic stroma 2. Still abundant
Late secretory (ovulation, normal lutein function). Fig. 2, right	1. "Saw tooth" glands with definite secretory activity	1. Epithelium papillary with formation of serrated glands 2. Nucleus basilar 3. Cytoplasm granular 4. Obvious secretory activity	1. Hyperemic and edematous 2. Less abundant 3. Early hemorrhage in outer layers

There are several methods by which a poorly functioning corpus luteum may achieve normal development in subsequent cycles:

1. Spontaneous.—The biopsy which demonstrates an early secretory phase may perhaps indicate only an unusual cycle, similar to the anovulation which may occur in normally ovulating women.[11] If such is the case, a subsequent biopsy should show full secretory activity. Conclusions which are drawn from multiple, similar biopsies are quite valid. On the other hand, unless the early secretory status is typical for the patient, this should not be a factor in her sterility problem.

Among some patients with this syndrome, pregnancy may sometimes follow an investigative procedure. It seems probable that cervical stimulation, perhaps by instrumentation, may produce changes in hormonal balance. This

mechanism may be similar to the copulation-ovulation sequence in the prolific rabbit. In any event, a return to normal progesterone elaboration may well occur without any specific therapy.

2. Thyroid.—Although the basal metabolism is an imperfect index of thyroid function, and although a negative report is reasonably common, subclinical hypothyroidism may be responsible for poor lutein function. Occasionally patients who are taking only thyroid became pregnant, and we are prone to assume the involvement of this relationship. On the other hand, thyroid is used more liberally than any other medication in this problem, and its over-all effectiveness certainly seems quite limited. Until a simple, accurate method to determine thyroid activity becomes available, a method which will be more practical perhaps than blood iodine studies, and more useful than radioactive iodine uptake is at present, the true association of the thyroid with this problem remains debatable.

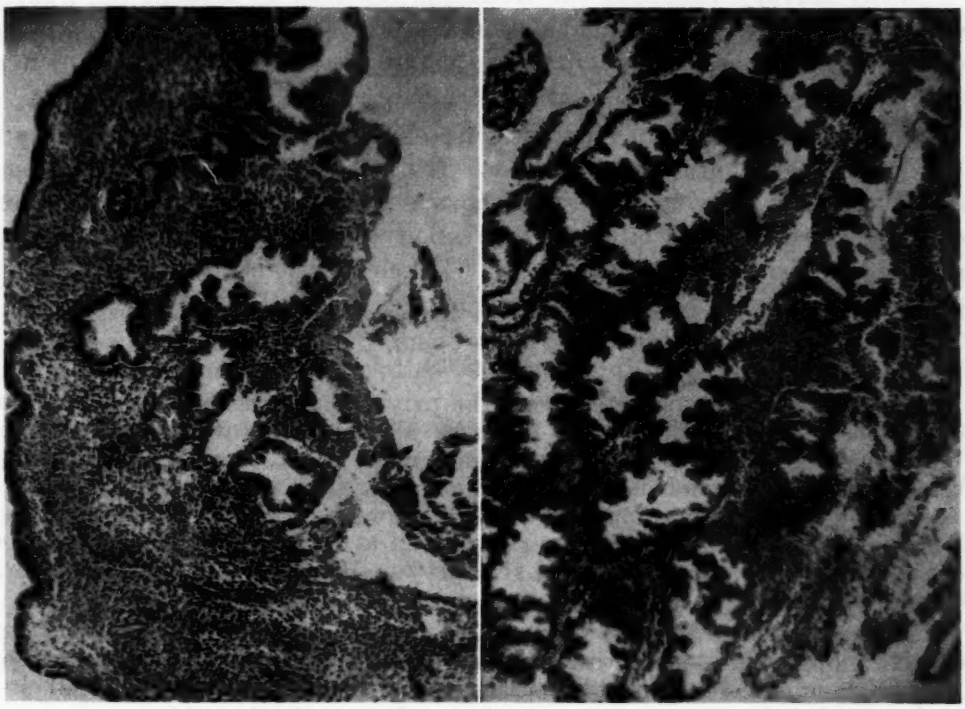

Fig. 2.—*Left,* Incomplete or early secretory endometrium. *Right,* Complete or late secretory endometrium.

3. Estrogens.—The estrogens in the normal hormone balance stimulate the pituitary to the production of luteotrophic hormone.[11, 12, 13] An attempt is made to simulate and reinforce this reaction when estrogens are used during the first half of the menstrual cycle. It is imperative that the dosage be small in order to avoid the inhibition of ovulation. Hughes[14] used this technique to increase glycogen levels in the premenstrual endometrium. He suggests 0.1 mg. of di-

ethylstilbestrol or an equivalent dose of other estrogens. The Smiths[15] suggest that the maximum dose of stilbestrol should not exceed 0.3 mg.

4. Cyclic Steroid Therapy.—Using estrogen followed by or given simultaneously with progesterone tends to supplement the endogenous ovarian hormones. This therapeutic technique finds its principal value among women with irregular cycles, since periods of withdrawal bleeding may be planned. It is suggested that after several courses a more regular pattern of menstrual bleeding may continue, perhaps with improved corpus luteum function.

5. Gonadotrophins.—The pituitary gonadotrophins have been used by us in a small series of patients. Both anterior pituitary-like substance and Hamblin's[16] "1-2" gonadotrophins have been tried. On the whole, these preliminary experiences have proved unsatisfactory, although our single patient successfully treated with gonadotrophins had a long history of infertility. More potent products and further investigations are urgently needed.

X-ray therapy following the technique reported by Kaplan for treating secondary amenorrhea and anovulation was used in two patients. Although one subsequently became pregnant and carried to term, it is obvious that no comment can yet be made.

Cortisone was tried in four patients. The rationale lay in the ability of this drug to cause pituitary depression. It was hoped that a release phenomenon would follow, during which more normal amounts of luteotrophic hormone would be secreted. The pituitary depression was achieved, and demonstrated in one of our patients by anovulation. The release phenomenon unfortunately was never evidenced. None of these patients was benefited.

Material

Our patients were selected from the private practices of four physicians, on the basis of their endometrial biopsies. The interpretation, "endometrium (menstrual) in an early secretory phase," made them eligible for this study. Almost all of these women had a complete infertility work-up. Our report is based upon the investigation of 75 women, from whom 130 biopsies were taken. Their ages varied from 19 to 39 years with an average of 28. The duration of their infertility complaints ranged from 1½ to 10 years, but the average was 4½ years.

This syndrome of lutein inadequacy was diagnosed from 29 of 112 consecutive biopsies taken from infertile women who consulted one of the authors (H. I. K.), an incidence of 25.9 per cent. Although the series is small, it is our impression that it may occur even more frequently than this.

Other factors which contributed to the infertility problems among the entire group were:

A. Sperm Deficiencies: In 15 men of whom 2 improved sufficiently for their wives to become pregnant.

B. Suspected Endometriosis: 4.

C. Tubal Occlusion (where patency could not be re-established): 1.

The temperature records were biphasic in 59 women, irregular or mixed in 9, and not given in 7. If menstruation may be considered to be regular when

the cycles vary less than seven days, then they were so classified in 55 patients. They were irregular in 20.

The history of previous pregnancies among the group was interesting. Twenty-eight of these women had 37 pregnancies before their infertility began. Only 18 children were liveborn. There were 17 spontaneous abortions and 2 ectopic pregnancies. Although a history of spontaneous abortion does not necessarily incriminate the corpus luteum, it does point to the need for an endometrial biopsy. In answer to our first question, therefore, this biopsy is the only clinically useful method of diagnosing an improperly functioning corpus luteum.

In order to facilitate this study, our patients were divided into three arbitrary groups:

A. Thirty-seven patients were subjected to multiple biopsies. Since 13 became pregnant, they also form part of the next group.

B. There were 25 patients who achieved 28 pregnancies (Table II). Seventeen were delivered of normal children and 5 are now still pregnant. There were 5 spontaneous abortions and 1 ectopic pregnancy. Carrying a pregnancy to term is the best evidence that lutein function has become adequate, at least to solve the patient's primary problem.

TABLE II. ANALYSIS OF 28 PREGNANCIES ACHIEVED BY 25 WOMEN, 33⅓ PER CENT

Children	17
Patients now pregnant	5
Spontaneous abortions	5
Ectopic pregnancy	1

C. Among 26 patients subjected to only one biopsy, the infertility persisted. Five of these cases were possibly explained by uncorrected sperm deficiencies, and one by tubal occlusion. In the remaining 20, it was considered probable that the poorly functioning corpus luteum was not influenced by treatment. Had it been possible to secure additional biopsies, they would surely have been informative.

Most of our patients received multiple therapeutic darts. In tabulating our results, these women are listed with several of the drugs under consideration. This will explain the apparent disparity when the totals exceed our 75 patients.

We all have the tendency to attribute the solution of a medical problem to the drug we are using at the time. However, it must also be recognized that a fruitful result may be due to a spontaneous change in physiologic circumstances, or even to the delayed activity of some therapeutic predecessor. Hence, when we indicate the agent which is responsible for success, it is often a human frailty, and not necessarily scientifically sound.

Results

The results of therapy are tabulated in Table III, and herein lies the answer to the second question. The 28 pregnancies among 25 women would indicate that, in the presence of the deficient corpus luteum syndrome alone, one woman in three may become pregnant. With adequate care, she will probably have an estimated 75 per cent chance for a live baby.

The third question may also be answered, to some extent, from this table. It is immediately evident that all of the recommended methods have some merit. The estrogens and the cyclic steroids appeared to be more effective

TABLE III. RESPONSE TO TREATMENT

DRUG	NO. PATIENTS TREATED	PREGNANCY	REPEAT BIOPSY, LATE SECRETORY
1. Thyroid	48	3	1
2. Estrogens	41	7	2
3. Cyclic steroid	29	6	1
4. Gonadotrophins	10	1	0
5. Cortisone	4	0	0
6. (Probable spontaneous*)	0	11	0
Total		28	4

*Includes investigation but no treatment. Cause for response unknown.

than the others. There is an urgent need for newer, potent preparations to treat this syndrome more effectively.

Summary

1. If an endometrial biopsy taken at the onset of menstruation reveals an early secretory pattern, it is good evidence of a corpus luteum deficiency.

2. Since blood levels of progesterone are not usually determined, this is the only clinical method by which this diagnosis may be established.

3. The incidence of this syndrome among infertile women is about 25.9 per cent.

4. Spontaneous return to normal corpus luteum function may occur.

5. The therapeutic agents which were occasionally successful were thyroid, estrogens, combined estrogen-progesterone, and gonadotrophin. Cortisone was unsuccessful in a small group of women.

6. The luteal deficiency syndrome may play a prominent part in a sterility problem. After investigation and treatment, one in three of our patients conceived.

We are grateful to Drs. Vieaux and Prejean for cooperating in this study, and to Dr. Cairns for his help and encouragement.

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Discussion

DR. HAROLD C. MACK, Detroit, Mich.—Unless a suitable bed is provided for its implantation, the fate of the fertilized ovum will be like that of seed sown on stony ground.

Complete failure of nidation or early, repeated abortions would seem to be inevitable if the lutein defect is consistent.

Evidence provided by endometrial biopsies, as well as other tests such as pregnandiol determinations and basal temperature observations, leaves little doubt that abnormal ovarian cycles do result from corpus luteum deficiency. How frequently such defective cycles occur among fertile women, how consistently they recur among sterile women, and what therapeutic measures will correct them are among the many questions which remain unanswered.

Like others, the authors also recognize the lack of completely reliable diagnostic methods. Even endometrial biopsy has only limited value since it is obvious that a poorly developed endometrium in one cycle does not necessarily indicate what will happen in the next. The endometrium at menstruation provides cytological evidence only of the ovarian balance of the cycle just completed. It is a record, as someone has said, "like the minutes of last month's mating." Moreover, it is recognized also that single strips of endometrium obtained by biopsy do not always give a clear-cut picture since the mucosa does not everywhere react with equal intensity and completeness. It is to be hoped that newer histochemical methods will some day permit a better evaluation of the ovarian endocrine impact upon the endometrium in certain phases which still trouble even expert histologists. The authors are fully aware of these and other pitfalls in making a diagnosis of lutein inadequacy except after "multiple" biopsies. Unfortunately, they do not indicate how many consecutive cycles were investigated to determine that lutein insufficiency was a consistent feature worthy of therapeutic efforts. The question arises as to how frequently this "syndrome" may occur even among fertile women, and whether like anovulation it is not often merely an intercurrent break in the ovarian rhythm. As such it would be at most a source of relative rather than actual sterility. In other words, there is reason for skepticism as to the necessity for treatment in many of these women. If we note that 12 of the 38 women with lutein inadequacy judged by a single biopsy achieved pregnancies, and also that 13 of the remaining 37 women who had had multiple biopsies were also successful, one might conclude that corpus luteum deficiency was not always an established pattern. This seems evident also from the fact that 11 of the 28 pregnancies followed no treatment at all.

Since corpus luteum failure is fundamentally a manifestation of pituitary rather than ovarian failure one might question whether anything more than temporary benefit could be derived from steroid supplementation. As the authors have stated, the need is for clinically effective gonadotropes; and they are not as yet available. In those instances in which consistent pituitary failure results in repeated lutein inadequacy some benefits might be derived from intensive efforts, such as suggested by Brown and Bradbury, to prolong the activity of the corpus luteum by large dosages of chorionic gonadotrophins; Fried and Rakoff recently attempted the administration of prolactin and chorionic gonadotrophin for this same purpose. If benefits are to be derived from therapy it would appear that we would expect them to lessen the incidence of early abortion. The problem of corpus luteum insufficiency is one of relative infertility rather than of primary sterility.

Drs. Kantor and Harrel have called this paper a "summary" of the problem which they have described. It shows clearly how much more fundamental knowledge is needed before we can discuss and treat this clinical entity with confidence.

DR. RONALD R. GREENE, Chicago, Ill.—I am not even certain that this would be particularly pertinent to the paper that has been presented, but Dr. Hisaw has done a great deal of fundamental work on the ability of the endometrium to respond to hormones, which reports have been confirmed by others. Apparently the endometrium will respond to estrogens only in a very limited manner, chronologically speaking; with continuous therapy it gives the full response over a period of 30 to 40 days. After that time it slowly and gradually regresses, even though the treatment is continued.

To get full response of endometrium, full growth of endometrium, progesterone is also necessary in small doses, added to the estrogen. In higher doses you cut down the mitotic figures as you get the full secretory response.

In examining a biopsy which is done as part of experimental studies or because the woman is bleeding too much, it is literally amazing how the different areas may vary in their response to hormones. A single strip biopsy is useful, but it does not necessarily give quantitative information as to the hormone levels in the body. Even if you have four strip biopsies, one still wonders, if they vary from normal, whether it is because the endometrium is not responding properly, or if the hormone is not being produced properly.

The thesis of this particular paper basically stands or falls on the interpretation of biopsies. The first biopsy as shown in the slide was to portray an early secretory or inadequate secretory response. I am sorry but to me it looked like a portion of endometrium from the superficial or compact zone after regression had taken place. The nuclei, as you noticed, were very close together. The glands were sparse only because the relative amount of stroma to glands is greater in the superficial portion of the endometrium. Photographs taken lower in the endometrium would show glands that are very much more profuse, and would give you a picture resembling that of the photograph on your right. The first biopsy does not represent a deficient progesterone but is just as normal a late secretory endometrium as was the second.

DR. KANTOR (Closing).—Our principal thought was to bring to mind the further use of the endometrial biopsy both to determine the presence or absence of ovulation and to get some concept of the ovarian hormonal balance.

All of these patients had correlated basal temperature graphs, and we did include these reports in the paper. There was no indication from the temperature graph that poor progesterone elaboration existed.

Dr. Greene points out that our biopsy photograph showing an early secretory pattern is questionable. I would like to state that it is difficult to photograph a single microscopic section and obtain from it a uniform interpretation, especially of endometrial phase. Our biopsies almost always represented a minimum of three strips from different parts of the uterus. They were all read by Dr. Cairns, a competent, qualified pathologist, so we believe that his interpretations of different biopsies were certainly comparable. It was because of this common denominator that we felt we were able to report this series with confidence.

I want to say that we do *not* know any specific or magic treatment for these patients, but we think that the syndrome of luteal deficiency is one which should be more widely recognized.

BILL'S MANEUVER IN RELATION TO PERSISTENT OCCIPUT POSTERIOR POSITIONS*

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IN 1919, Dr. John Hirst[1] of Philadelphia wrote in his *Manual of Obstetrics* that there were three conditions that we dread in the management of the occiput posterior. They were: (1) increase in uterine inertia, (2) increase in lacerations of the perineum, and (3) increase in fetal mortality. He listed the latter at 9 per cent. There are other conditions which arise at times during these labors that cause us concern but less often and possibly not as much as these three. I believe that most of us dread seeing the waiting family as much as managing the patients, especially where we are confronted with uterine inertia to prolong this misery for all concerned.

In preparation of this paper, we have chosen the case records of patients delivered by us in the years 1949, 1950, and 1951. These comprise approximately 1,500 private patients, most of these having been delivered by the senior author. Although this is not a great number, we felt this would give a fair over-all picture and would be a reasonably comparative group for those present here.

Incidence

In this group of patients, we found that we had 76 cases which presented the persistent occiput posterior, or 5.06 per cent (Table I). This is slightly higher than the average, given as 3.8 per cent. This is possibly due to the fact that it is our policy to rotate our occiput posteriors earlier than many who practice obstetrics and for this reason we diagnose the position early while some of these presentations might rotate spontaneously and not be detected otherwise.

There were 67 per cent in right occipitoposterior and 25 per cent in left occipitoposterior. Five per cent were direct posteriors. Two per cent were brow presentations or nearly so. These are listed since they were handled just as the true posteriors were. As you will see, many of our patients had uterine inertia which is always a common problem in the occiput posterior position. We reviewed the type of pelvis found in these cases and failed to find any association of the position of the fetal head with any particular class of pelvic structure.

It is our impression that occiput posterior presentation occurs either because the pelvis is small with a relatively large fetal head for that particular patient, which prevents rotation, or because of a large pelvis with a relaxed perineum, the soft tissues of which fail to offer enough resistance to aid rotation and the fetal head merely "falls into the large roomy pelvis." . . . We have

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had occasion to deliver four of our patients with the fetal head in the posterior position, two or more times. We failed to detect any peculiarity which might account for this; however, these cases have not been studied in detail.

Neither size nor age of the patient seems to play any part as some were obese and others of a tall slender build. We have delivered posteriors in patients from the age of 11 years on up through the childbearing years.

Inertia and prolonged labor have always been our greatest problems and I would assume this is the case with everyone here. We had an incidence of 38 per cent. This being a subject in itself, I will not discuss it further, except to say that apparently the position of the fetus gives rise to faulty uterine contractions.

TABLE I. RELATIVE INCIDENCE

	NO.	PER CENT
1. Total number of cases reviewed	1,500	
2. Number of persistent occiput posteriors	76	5.06
a. Number of R.O.P.	51	67.1
b. Number of L.O.P.	19	25.0
c. Number of O.P.	4	5.26
d. Number of brow presentations	2	2.63
3. Total number with prolonged labors	30	38.0
4. Total number with repeated posteriors	4	
5. Total number of primiparas	47	61.8
6. Total number of multiparas	29	39.2

Now, I wish to discuss the management of occiput posterior when once full dilatation has occurred or is near enough to carry out the delivery without any real damage to the mother or infant. If the cervix is almost completely dilated, and the fetal head is at or below the midpelvic plane, I feel that it is not poor obstetrics to incise the cervix under careful scrutiny, and complete the delivery if this is urgent due to fetal or maternal indications or both. I refer chiefly to those cases where there is a thick but narrow rim of edematous cervix left which is the obstructive agent. Sometimes this can be pushed out of the way without much difficulty or actual lasting damage to the cervix. If the cervix is only 6 to 7 cm. dilated and delivery is urgent, I certainly would prefer the proper abdominal approach.

It has been stated[2] that all except 10 to 20 per cent of occiput posteriors will rotate spontaneously to an anterior or transverse position. Of the persistent cases, about half will deliver spontaneously, but for the rest, operative intervention will be necessary.

As will be seen in our series, we did not find this to be true. Maybe this is due to the fact that it is our practice to intervene sooner than is commonly done by most of those present. It is our policy to rotate our posteriors when the cervix is fully dilated if labor appears at a standstill for a period of one or two hours. We do not believe that waiting proves to be the safest measure but rather that an early end to the labor process will be more desirable for the exhausted mother and may better protect the infant involved. We would therefore recommend forceps rotation to bring about the termination of labor to those who are skilled in forceps management.

We do not want our posteriors to rotate to transverse as this certainly presents a more difficult problem for us. It is our opinion that the transverse position definitely offers more trouble at delivery and that the end results are fraught with greater dangers. Nor do we like to attempt to rotate the occiput posterior manually as we have most often changed it only to a transverse position which we wanted to avoid. On an occasion, we have had a prolapse of the cord by such method, only to add fright to uneasiness.

Technique

As seen in Table II, 73 per cent of our cases were rotated by forceps and only one manually. Two were delivered as posteriors, why, I cannot recall. We do not like the latter method as this requires more trauma to the fetus in most cases due to lack of pelvic room and, as is generally recognized, gives rise to a greater incidence of soft-tissue damage.

TABLE II. METHODS OF DELIVERY

1. Rotation by Bill's maneuver	73
2. Manual rotation	1
3. Delivered as posteriors	2

For our rotations, we prefer the maneuver described by Dr. Arthur Bill of Cleveland, Ohio, about 1931. We use this because of the ease with which it can be executed. This is a modification of the "old Scanzoni maneuver," the real difference being that the head is rotated higher in the pelvis where there is more room and this can be done with greater freedom. I wish to describe briefly this maneuver. The forceps is applied to the fetal head as if it were in the anterior position. The head is then pushed upward in the pelvis, thereby being taken to the greater diameter of the pelvis at or near the inlet. The head is flexed as this is done. Then, with a gradual swing of the forceps, the head is rotated through an angle of 135 degrees, going from a right occipitoposterior to a right occipitoanterior or left, as the case may be. When the head is rotated as desired, a gentle traction downward is used to fix the head in the pelvis again. The assistant is then asked to keep firm pressure on the fundal portion of the uterus while reapplication of the forceps is being accomplished. Many times we leave one blade of the forceps in place and introduce the removed blade by the side of this so as to prevent the head from reverting to its former position. This, of course, is facilitated by the fundal pressure of the assistant. When both blades have been properly reapplied to the satisfaction of the operator as evidenced by careful rechecking of the position of the fetal head, the delivery is completed.

We are cognizant of the method used by King and his associates[3] which appears to be different from the one described above only in that they do not remove the first blade from the vagina while reapplication is carried out but merely sweep this blade to the opposite side. They believe this to be more effective in preventing the fetal head from slipping back to its original position. We have not used this method but certainly can appreciate its merit.

We prefer the Tucker-McLean forceps or some forceps with only slight modification of the Tucker-McLean.

Our reasons for choosing this forceps are mainly two: the long leverage afforded and the close application of the blades to the fetal head. We have used other forceps such as Simpsons' or Elliotts', only to be handicapped by the lack of leverage of these short blades. We have attempted to use the Kielland forceps on numerous occasions and here we were presented with the problem of the forceps rotating easily but the fetal head remaining in its original position or at other times we found that this forceps would slip on the fetal head when downward traction was made for extracting the fetus. This is due to the shallow cephalic curve present with this forceps.

With a maneuver that displaces the fetal head upward in the pelvis, one might readily expect that prolapse of the umbilical cord would be a constant dread. We have never encountered this in any of the cases reviewed or in any of the cases handled by this maneuver in the past 10 to 12 years during which I have been using this method of handling the occiput posterior position. I

would estimate that during this time between two and three hundred cases have been managed in this manner. However, I can recall having a cord prolapse many years ago when I was in my early years of obstetrics, while attempting to rotate a posterior manually. This caused me a few very anxious and fearful moments while I tried to handle two problems at once. This instance, although it did not end in loss of the infant, possibly is partly the reason why I became interested in another procedure. This case is one of the last if not the last one I have ever rotated by hand. I believe there is ample logic to suggest that the forceps blades being applied to either side of the fetal head will fill the space left in the pelvis sufficiently to prevent the cord from dropping down beside the fetal head as it is displaced upward during the rotation described.

Maternal Complications

As will be noted in Table III, we have had little worry from this angle. There were 7 cases which had extensions of the episiotomy or small vaginal-wall lacerations confined to the mucous membrane and contingent tissues. I believe these occurred principally during the extraction of the fetus after rotation and not during rotation. If I am correct in this assumption, one would certainly expect this to be a greater problem had the fetal head been extracted as a posterior. Twice in this series of patients enough damage to the cervix was done to require special attention. This might have been avoided had we not used this method of rotation; however, this is not an infrequent complication in many deliveries, normal or abnormal. We were not confronted with any actual postpartum hemorrhage, injuries to the bladder, or third-degree lacerations of the perineum. It is my impression that the latter are encountered more often when the method of extracting the fetus as a posterior is resorted to. Recently, Randall[2] reviewed a much larger series of cases which appeared to be handled in a different way for the most part. In his group, he listed the following incidence of these maternal complications: complete lacerations of the perineum, 1.06 per cent, and postpartum hemorrhage, 7.43 per cent.

Had we reviewed all of our cases for the past 10 years, I feel sure we would have found an occasional case where there was an excess blood loss as this is inevitable in obstetrics and is certainly more likely to occur where one is dealing frequently with inertia of the uterus. I do not believe we have ever had a complete laceration of the perineum in any of our patients where this method of treatment for the posterior has been used. We had no maternal deaths or postpartum sequelae of note.

TABLE III. COMPLICATIONS OF ROTATION

1. Maternal mortality	0
2. Fetal mortality	0
3. Injuries to infant	0
4. Injuries to mother	
a. Extension of episiotomy	7
b. Lacerations of cervix	2

Fetal Complications

Fortunately, on this subject there is little to record. There were no fetal deaths and as far as we know no fetal injuries. Until recently, I have not been cognizant of having had a fetal injury; however, just a few months ago a fracture of the clavicle occurred in a large infant with large shoulders who was rotated from the posterior position. I felt that this could be attributed to the size of the shoulders instead of the rotation, Maybe not. In reviewing the literature, we found fetal mortality ranging to as high as 9 per cent (Hirst).

Conclusion

We have presented a group of 76 patients with the occiput posterior position of the fetal head, encountered by us in our private practice over a period of three years. This represents an incidence of 5.06 per cent.

The method of delivering these patients has been presented. We choose to use the Tucker-McLean forceps for rotating the occiput posterior. Our reasons have been listed.

The complications have been minimal. There were no serious maternal complications. There were no fetal deaths and, to our knowledge, no fetal injuries.

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Discussion

DR. G. KEITH FOLGER, Cleveland, Ohio.—My chief, Dr. Arthur H. Bill, taught that any procedure which shortened the mother's discomfort, decreased her complications, and benefited the baby was worth very careful consideration. He would never sanction for one moment the thought that any baby should be sacrificed, if this could be prevented by an operative procedure.

I would like to stress the importance of accuracy and fairness in our teaching on the graduate and postgraduate level. As an example, Eastman's *Williams Obstetrics*, page 1076, describes the Scanzoni as follows, "After applying the forceps a downward traction is then made, and at the same time a rotary motion is imparted to the forceps, when the head slowly descends and rotates to a right transverse, and later on when it impinges upon the pelvic floor further rotation occurs to an obliquely anterior position." Contrast that to Reddoch's translation of Scanzoni's own description of this rotation and I quote, ". . . an eighth of a circle is now described with the instrument: . . . and in this way, the head is rotated." Then, "Both blades are removed, and again reapplied, whereupon by the next rotation the occiput is brought completely under the pubic arch." Nothing is said about a downward traction with a rotary motion to accomplish the rotation. Inaccurate and deprecating statements have no place in medicine. To condemn a procedure without a thorough knowledge and trial of it is to admit one's lack of training in the procedure or a blind prejudice against it.

Hellman, in his article, "The Duration of the Second Stage of Labor," refers to Holland's description of the death of Princess Charlotte of Wales in 1817, as a graphic portrayal of the blind faith in nature and the supine inactivity of the obstetricians of that day. He also graphically shows the increased mortality of the babies and the increased morbidity of the mothers after two and one-half hours of second stage. We feel the time to rotate a posterior in the second stage has arrived when the head no longer descends with pains or retracts between pains. This is especially true in a multigravida who had normal labors with her prior deliveries when the occiput was anterior. Even in the hands of our resident staff we have not seen tears of the vagina or cervix due to the rotation. In the primigravida it is even more important to rotate before the head is wedged under the symphysis. This saves the soft tissues and requires much less force on the fetal head for delivery. Hellman, Willson and Alesbury, Winterringer and others have recently shown the results of prolonged labor. I cannot help but feel that as our studies go forward toward the greater salvage of babies, we will be more conscious of the effects of these longer labors on babies who survive but show behavior problems of varying degrees later in childhood. I cannot see the logic of prolonging any labor in which the fault lies with a faulty position of the baby. Positional dystocia is one of the most frequent causes of pro-

longed labor. When one sees the ease with which a head will descend after being rotated he will never subject the baby or mother to the forces necessary to accomplish delivery with the occiput posterior.

Dr. Greene has confined his paper to the discussion of the management of the occiput posterior when once full dilatation has occurred or is near enough to carry out the delivery without any real damage to the mother or infant.

I would like to ask Dr. Greene in how many cases in this series there was a thick edematous rim of cervix which had to be cut or lifted up out of the way. I find in my own practice this condition is becoming very much more rare. This type of case demands the best of one's ability and judgment. After a long first stage the mother is weary and the fetus is beginning to show signs of distress. To increase the force of the pains by stimulation often produces a marked slowing of the fetal heartbeat and more distress to the baby. Further sedation likewise produces more anoxia. Operative interference should not be delayed until it has no chance to succeed. Incision of the cervix is very infrequently employed by us but certainly it is a lifesaving measure at times.

For those interested, I would like to refer you to Volume 2 of *Obstetrics and Gynecology* by Carl Henry Davis, pages 41-50, for a beautifully illustrated description of Bill's maneuver for rotating the occiput posterior.

DR. ALWYN E. BENNETT, Cleveland, Ohio.—There are a few points I would like to make as to the handling of these patients, made necessary by the increase in use of spinal anesthesia in these last few years, particularly in patients with ruptured membranes.

Turning the baby with this maneuver, when the patient's head and shoulders are raised, offers some resistance at times. I have managed to get rid of this difficulty simply by lowering the patient's shoulders during the time of rotation. The head goes around to an anterior position and the shoulders then usually follow. As soon as the baby's occiput is anterior, the patient's shoulders are again raised, and delivery is then made without difficulty.

DR. ISADORE DYER, New Orleans, La.—I believe that in occiput posteriors, we can group a great number of those patients who give us some difficulty, and particularly those with prolonged labor.

I was very happy, for one, to hear Dr. Greene admit—and endorse, with reservations—the use of Dührssen's incisions in patients who, for some reason, cannot deliver the baby promptly, when immediate delivery is indicated.

It has been our experience—and yours, I am sure—that frequently one of the things that bother us in persistent occiput positions is the fact that the cervix will never completely dilate, and, if one waits solely for the disappearance of the edematous anterior lip, there have been occasions in our experience wherein the anterior lip has literally sloughed off.

I believe that there is an answer to the reason why posteriors persist, and I am of the opinion that there are two main factors. One is the size of the baby's head, the other, the actual configuration in measurement of the mother's pelvis, and particularly the midplane.

Saddle block anesthesia has been more or less eliminated in our private experience, because of the fact that the posterior position seems to be more frequent. The fetal heart tones frequently varied with the block and when one had to deliver the baby frequently one had to perform many midforceps deliveries.

Dr. King's maneuver—which I was privileged to collaborate with—is precisely the same as Bill's maneuver, with the one exception that the blade on the patient's left is the last one to be removed, and is not completely removed from the vagina but is just merely flipped around to the other side. That is just a minor difference.

As far as the blades are concerned—in contrast to Dr. Greene—we prefer a fenestrated blade. For a number of years we have used the DeLee modification of the Simpson. I be-

lieve a fenestrated blade, particularly in a difficult delivery, fits the baby better, and I believe, if you have a rather hard pull, this is a superior blade, at least it is in our hands.

I was interested in the two brow positions reported by Dr. Greene. We think at the moment that a brow presentation and forceps present just about the most "concentrated dynamite" that an obstetrician can contend with. I wish to know in detail how those two brow presentations were handled.

We did have a patient with transverse presentation deliver spontaneously on one of the charity services two years ago. It was a very small baby, and the patient literally precipitated.

Last, I am a little confused. We have here presented 1,500 deliveries with no fetal deaths. I would like to ask Dr. Greene if those figures have not been corrected, because in our own experience we have at least a 0.9 per cent fetal mortality from the abnormal babies, which I am sure you must run across in a practice like that.

DR. GREENE (Closing).—In connection with the remarks by Dr. Folger, I was glad that he stated that he did not believe that the rotations caused the extensions and lacerations of the vagina, etc., and also to see that they were using the Tucker-McLean forceps, which I endorse.

He asked how many cases of edematous cervix we had. I believe there were only one or two.

I feel that general anesthesia certainly is the choice of anesthesia for the rotation of posteriors. I would not like to use spinal anesthesia unless some unusual situation existed.

I was pleased to know that someone else had occasion to use Dührssen incisions.

There is a modification of the Tucker-McLean forceps which has a partial fenestration, but not a true fenestration, and I really prefer that blade over the one that is the solid blade all the way through.

As to the brow presentations, as I recall, they were posteriors with the brow presenting somewhat more than the occiput.

I talked about the fetal deaths only in the posterior group. I did not say there were no fetal deaths in 1,500 cases. We did not go into the fetal mortality of the whole group of patients.

Original Communications

STUDIES OF THE EFFECTS OF DIURETIC AGENTS ON EXCRETION OF WATER, SODIUM, POTASSIUM, AND NITROGEN IN PREGNANT PATIENTS

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(From the Departments of Obstetrics and Gynecology and Nutrition, State University of Iowa Hospitals)

ALTHOUGH the etiology of pre-eclampsia is still unknown, maternal morbidity and mortality from this disease have been greatly reduced by improved symptomatic therapy. One of the most important factors in present-day management of pre-eclampsia is the use of diuretic agents along with low-sodium diets to produce a more negative water and sodium balance.

The amount of investigative work which has been done to show the relative effectiveness of various diuretic agents in pregnancy is rather limited. Brown and Bradbury[1] compared the effects of various diuretic agents on urinary volume, and on sodium and chloride excretion in normal and toxemic patients, but did not demonstrate the action of diet alone over a comparable control period. They gave diuretic agents for 1 to 3 days and found transitory effects with a tendency toward a compensating retention of sodium after therapy was discontinued. Studies on the diuretic and antidiuretic properties of depressant drugs used in the toxemias of pregnancy have been presented by Brown, Hodges, and Bradbury[2] and others.[3, 4] These workers concluded that the narcotics tested were antidiuretic while hypnotics lacked this effect.

It appeared worth while to study the action of various diuretics in pregnancy over a longer period and with additional controls. The agents were compared on the basis of their influence on the excretion and balance of water, sodium, potassium, and nitrogen. The effect on potassium excretion and balance was of interest, considering that sodium, when present in excess amounts, may gradually replace intracellular potassium. Dieckmann[5] points out that the patient may be storing excessive amounts of sodium by this mechanism without any evidence of pitting edema. Since the accumulation of edema fluid or the retention of sodium may produce an alteration of protein metabolism, the relation of diuretic agents to nitrogen balance was also studied.

Materials and Methods

Diets.—The diets for this study were prepared by the Department of Nutrition. One diet produced a neutral ash and the other an acid ash equivalent to 28 c.c. of normal acid per day. Each diet included three different daily menus

so that each was repeated every third day. Sodium, potassium, and nitrogen values for each diet were determined on aliquots of several beaker meals of each menu. The daily sodium, potassium, and nitrogen levels in the neutral diet were 1.608, 4.280, and 20.45 Gm., respectively; for the acid-ash diet they were 1.662, 3.225, and 19.20 Gm. Caloric values, calculated from tables, were 1,898 for the neutral diet, and 1,828 for the acid-ash diet.

Patients.—The patients used for this study were hospitalized on the obstetric service and were under the supervision of a special nurse. Thirty-seven patients, three of whom had typical pre-eclampsia, were kept on these diets for 14 days. The neutral-ash diet served as a 14 day control. Other patients on the same diet were given a diuretic agent from the sixth through the tenth day. One patient on this diet was given magnesium sulfate parenterally. The acid-ash diet was given for 14 days without any additional diuretic agent, and the effects were compared with those of the control diet.

Fractional urine collections were made on the normal patients receiving ammonium chloride or 1 c.c. Mercuhydrin per day. On the remainder of the patients urine was collected daily as a 24 hour specimen.

Analyses.—Excretion studies were based entirely on urinary analyses, but balance determinations were calculated from the amounts of water, sodium, potassium, and nitrogen in the diet, urine, feces, and emesis (which occurred in 3 patients), taking into account the amounts in fluids and food refused by the patients. Values for the feces were determined by taking a daily average for all feces excreted in each period, viz., the initial 5 day control period, the 5 day diuretic period, and the final 4 day control period. Urinary pH, ammonia, titratable acidity, and creatinine were also determined, and, when relevant, blood urea nitrogen and carbon dioxide combining power in addition. The patients were weighed each day to the closest 0.25 pound.

Materials Studied.—The following diuretics were given for five consecutive days:

1. Ammonium chloride, 25 5 gr. tablets per day (8.1 Gm.) in 3 divided doses at 7 A.M., 11 A.M., and 3 P.M.

2. Mercuhydrin (mercurial 88 mg. per c.c. plus theophylline 48 mg. per cubic centimeter) intramuscularly, in doses of 1 to 2 c.c. at 7 A.M. each day.

3. Magnesium sulfate, deep intramuscularly, 10 c.c. of a 50 per cent solution every six hours.

Results

Excretion Studies.—

Creatinine values which attested to relatively complete urine collections averaged 1.21 Gm. per day with a standard deviation of 0.33 Gm. per day. The average excretion data with pertinent standard deviations from the sixth through the tenth days when a diuretic agent was used, and for all 14 days for the control and acid-ash diets were determined but are not included in this publication because of the large volume of material. However, some of these data are presented graphically in Figs. 1 and 2. The data for magnesium sulfate and Mercuhydrin (2 c.c. per day) are not graphed due to the limited number of runs.

Controls.—The urine volume for the control patients continued to fluctuate over the 14 day period, whereas sodium excretion decreased for the first 6 days, and gradually rose after the eighth day. No fall occurred in the control potassium excretion until the fifth day; a gradual rise occurred after the sixth day. Ammonia excretion and titratable acidity were reasonably constant over the entire period. In general, it appeared to take 6 days for the patients to adjust to this low-salt diet.

Ammonium Chloride.—In both normal and pre-eclamptic patients the ammonium chloride gave a marked peak on the second day for the amount of urine, sodium, and potassium excreted. The urine volume for the normal patients receiving ammonium chloride was increased over the control level by more than one standard deviation on the second and fourth days. It did not give a significant (for the purposes of this paper assumed to be any change greater than one standard deviation) increase in urine volume for the entire 5 day diuretic period, nor did any of the other diuretics tested. The excretion of sodium was significantly increased for the whole period of ammonium

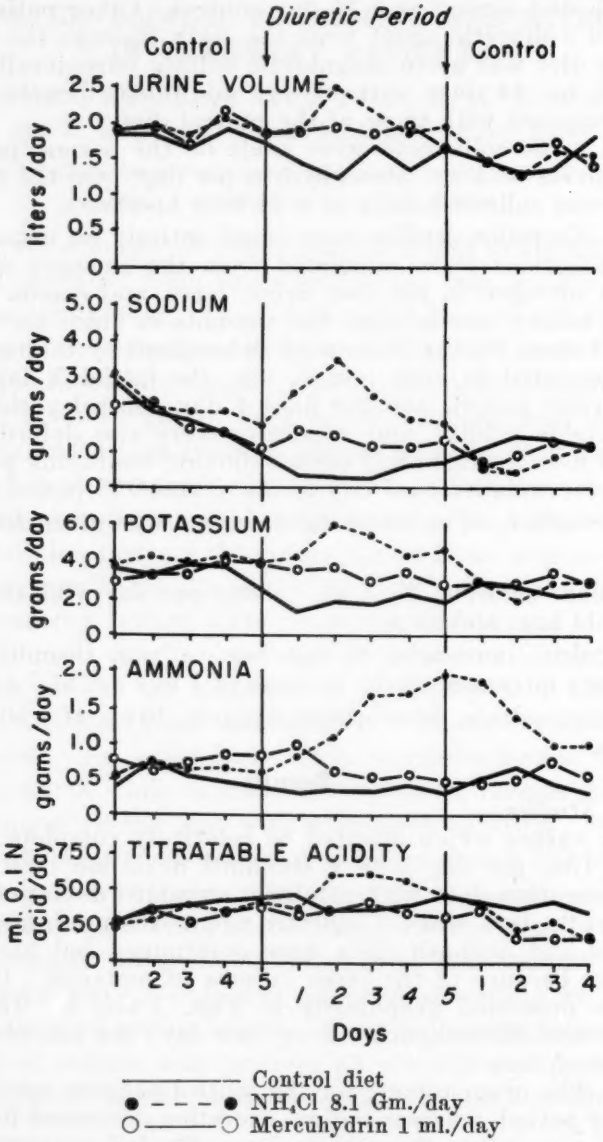

Fig. 1.—The curve for control diet represents average values for observations on 5 normal pregnant patients during a 14 day period. The curves for ammonium chloride and Mercuhydrin show average values on 8 and 10 normal pregnant patients, respectively, all of whom were on a control (low-sodium) diet. The diuretic agent was given during the 5 day interval after an initial 5 day control period. Under these circumstances ammonium chloride was more effective in causing a loss of water, sodium, and potassium than was Mercuhydrin.

chloride therapy, in both normal and pre-eclamptic patients, and varied by more than three standard deviations in the normal patients on the second day. A significant increase in potassium excretion occurred for the 5 day period with the normal patients, but did not with the pre-eclamptic patients. Ammonia excretion lagged behind that of sodium and potassium, reaching a peak on the fifth day of ammonium chloride therapy. This increase was significant for the whole diuretic period except for the first day with pre-eclamptic patients. Titratable acidity increased until the third day with the normal patients and until the fifth day with the pre-eclamptic patients. In both types of patients the pH fell from the control level of 6.2-6.4 to 5.6 during the diuretic period and then rose to 6.2 by the fourteenth day. The total 14 day

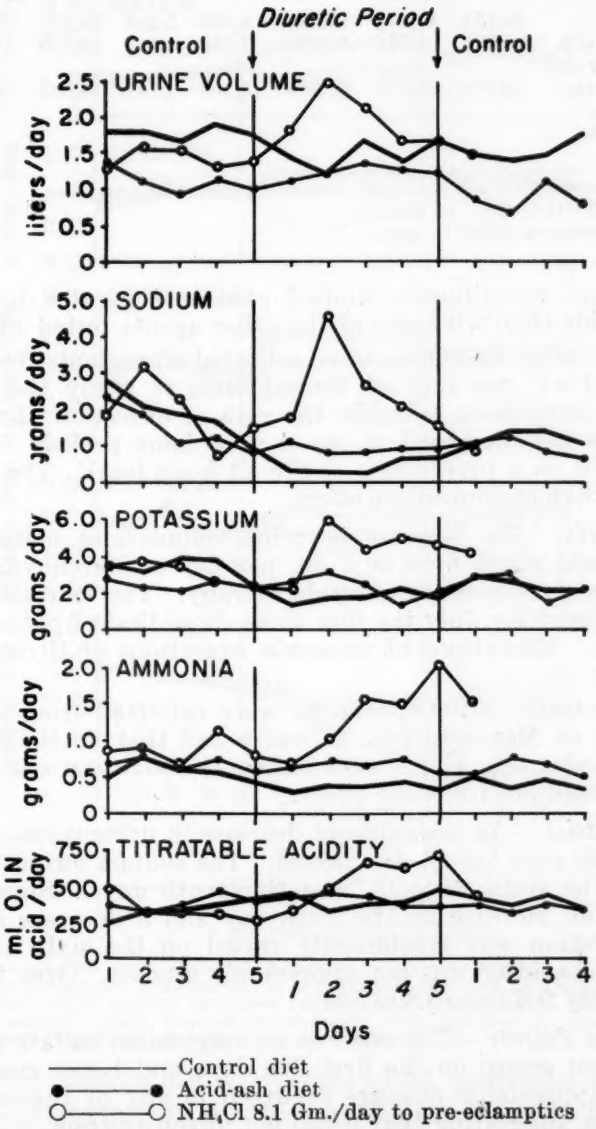

Fig. 2.—The control diet curve above is duplicated from Fig. 1. The acid-ash diet given to 10 normal pregnant patients did not produce any marked deviation from the results obtained with the control (low-sodium) diet. Three pre-eclamptic patients given ammonium chloride during the diuretic period exhibited similar increases in urine volume and in sodium and potassium excretion as the normal pregnant patients in Fig. 1. The acid-ash diet failed to duplicate these changes.

TABLE 1. TOTAL EXCRETION AND NET BALANCE (PER PATIENT) OVER THE 14-DAY PERIOD

	URINE VOLUME (C.C.)	SODIUM (MG.)	POTASSIUM (MG.)	AMMONIA (MG.)	TITRATABLE ACIDITY	*WATER	SODIUM (MG.)	POTASSIUM (MG.)	NITROGEN (GM.)
Controls	22,124	16,942	35,552	6,460	5,370	22,125	3,507	13,189	75.9
Ammonium chloride 8.1 Gm. per day	24,931	26,589	54,507	15,688	5,363	17,605	−7,177	−3,461	32.3
Mercuhydrin 1 c.c. per day	25,020	19,070	45,874	8,997	4,243	18,626	2,747	6,754	64.8
Mercuhydrin 2 c.c. per day	19,337	19,301	44,942	5,385	5,669	21,409	1,719	9,170	53.0
Acid-ash diet	15,151	16,073	33,362	9,163	5,495	18,228	7,321	10,065	65.4
Magnesium sulfate† 40 c.c. 50% per day	12,190	4,515	31,680	7,500	4,120	14,720	11,565	7,610	39.8
Ammonium chloride‡ 8.1 Gm. per day to pre-eclamptic patients	18,219	23,173	42,906	12,106	4,741	15,386	−6,360	2,286	48.0

*Water balance does not take into consideration insensible loss.
†Patient delivered after 13 days.
‡Patients delivered after 11 days.

excretion of all constituents studied exhibited greater increases with ammonium chloride than with any of the other agents tested (Table I).

Fractional urine specimens were collected on patients receiving ammonium chloride and 1 c.c. per day of Mercuhydrin to study the rapidity of their actions. For ammonium chloride, the rate of excretion of water, sodium, or potassium was not increased in the 4 or 8 hour periods following therapy, when compared as a percentage of the 24 hour total. This suggested a sustained rather than an immediate effect.

Mercuhydrin.—The increase in urine volume and sodium and potassium excretion brought about by 1 or 2 ml. per day of Mercuhydrin was much less marked than with ammonium chloride therapy. The increase in sodium excretion was significant for only the first three days, that of potassium for only the first two days. Alterations of ammonia excretions or titratable acidity were not significant.

When fractional urine specimens were collected from patients reeciving 1 c.c. per day of Mercurhydrin, it was found that, in the 8 hours following therapy, approximately 47 per cent of the 24 hour total sodium was excreted, suggesting a rapid but transient effect.

Acid-Ash Diet.—An insignificant decrease in urine volume was produced by the acid-ash diet over the 14 day period. The sodium output was significantly increased on the sixth, seventh, and thirteenth days. Significant potassium changes were an increase on the sixth day and a decrease on the ninth day. Ammonia excretion was significantly raised on the sixth through the tenth days; titratable acidity was not appreciably altered. Over the 14 day period the pH gradually fell from 5.8 to 5.3.

Magnesium Sulfate.—The one run on magnesium sulfate gives values lower than the control group on the first five days and hence cannot be compared with it. No appreciable changes occurred in any of the analyses when the drug was given, suggesting that it did not affect diuresis.

Balance Studies.—

The average data for the balance studies, along with pertinent standard deviations, are not included in this publication because of the large volume of

data. Some of the results are graphed in Figs. 3 and 4 except for those on magnesium sulfate and 2 c.c. per day of Mercuhydrin.

Controls.—The control diet gave a positive water balance throughout the 14 day period, rising gradually for the first 6 days, leveling, and then decreasing slowly after the ninth day. Sodium and potassium retention increased for 6 days, leveled off, and fluctuated somewhat after the tenth day. A positive nitrogen balance with moderate variations was maintained throughout the

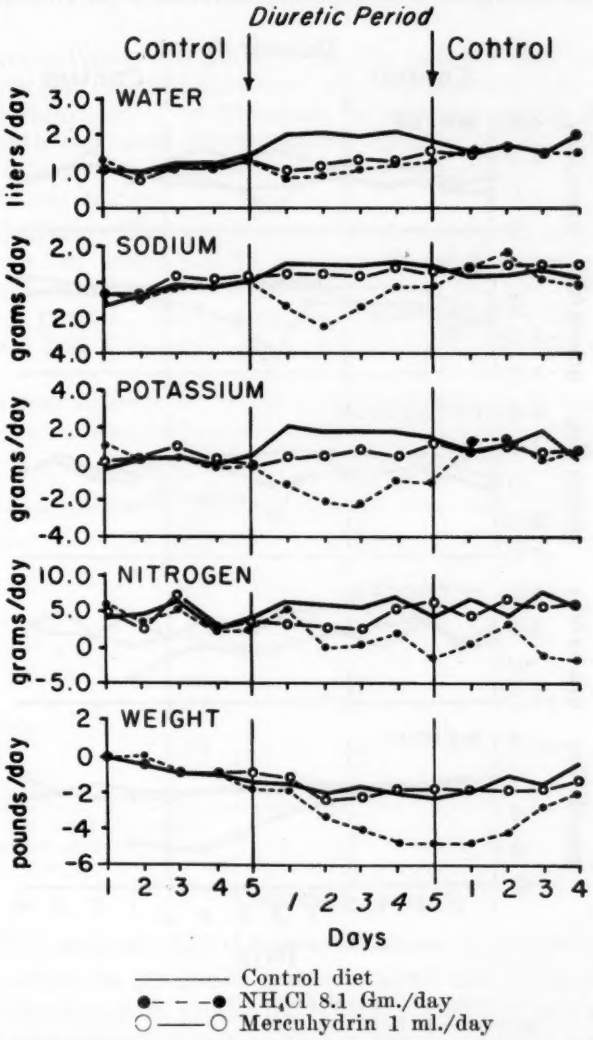

Fig. 3.—Balance studies were made on 5 normal pregnant patients given a control (low-salt) diet, on 8 normal pregnant patients given the control diet and ammonium chloride during the diuretic period, and on 10 normal pregnant patients given the control diet and Mercuhydrin during the diuretic period. Only ammonium chloride was effective in producing significant changes in the balance of sodium, potassium, and nitrogen.

entire period. The patients lost an average of 2.1 pounds on this diet during the first 10 days, then regained all but 0.3 pound of it by the end of the fourteenth day. These weight changes were roughly proportional to the changes in sodium and potassium balance.

Ammonium Chloride.—In both the normal and pre-eclamptic patients ammonium chloride decreased water balance maximally on the second day of its

administration, but the balance remained positive. The decrease was greater than one standard deviation in the normal patients for the first 2 days and in the pre-eclamptic patients for the first 3 days. A negative sodium balance was achieved over the entire diuretic period with ammonium chloride in both the normal and pre-eclamptic patients, whereas the control patients were in positive balance for the period. The shift of sodium balance was significant over the entire diuretic period for both types of patients. The potassium balance was also negative (compared to positive balance with control patients), the

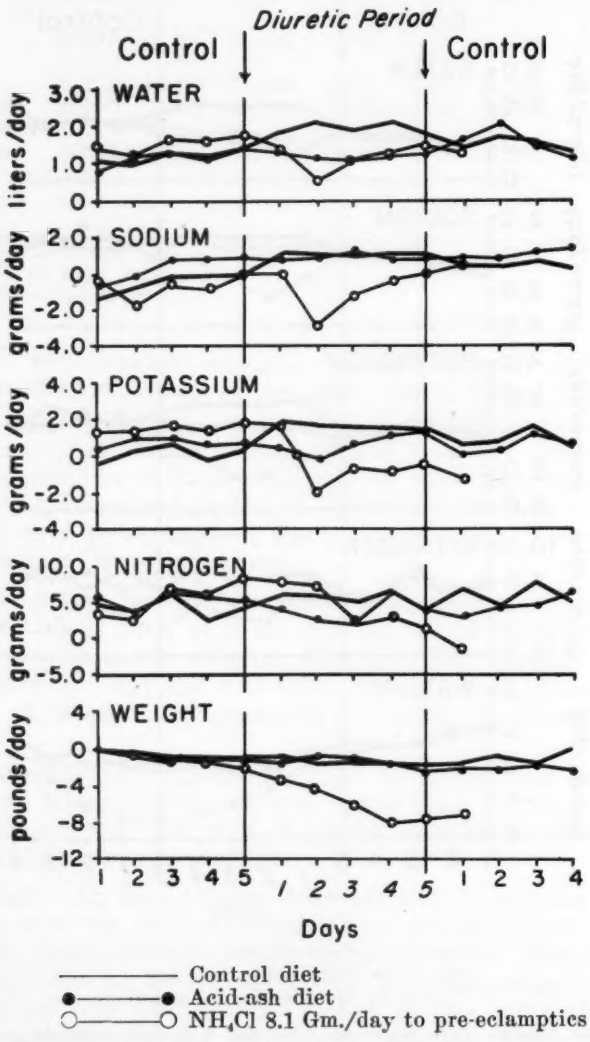

Fig. 4.—Ammonium chloride was effective in inducing a negative balance of sodium, potassium, water, and nitrogen in 3 pre-eclamptic patients. The control and acid-ash diets alone produced no significant balance changes in normal pregnant patients.

change being significant except for the first, fourth, and fifth diuretic days with the pre-eclamptic patients. The nitrogen balance was lowered, but to a significant degree on only the second and third diuretic days. The normal patients lost an average of 3.2 pounds during the diuretic period (Table II) while the pre-eclamptic patients were losing an average of 5.6 pounds. Both had a negative weight change over the 14 day period.

Mercuhydrin.—The diuretic effects of either 1 or 2 c.c. per day of Mercuhydrin were less than that of 8.1 Gm. per day of ammonium chloride, and lasted for only the first 3 days. The water balance was significantly decreased on the first day, potassium balance for the first 2 days (1 c.c. Mercuhydrin) and sodium balance for the first 3 days. Negative sodium balance was not attained.

No appreciable alteration of nitrogen balance occurred, but the patients on 1 c.c. per day lost 1.0 pound and those on 2 c.c. per day 3.3 pounds, for the diuretic period. They lost 1.5 and 3.2 pounds, respectively, for the 14 day period.

Acid-Ash Diet.—When compared with the control diet over the 14 day period, the acid-ash diet showed only very slight diuretic action. The water balance was reduced significantly on the sixth through the eighth days, the sodium balance on the sixth day, and the potassium balance on the sixth and seventh days. Nitrogen balance was not altered. The patients lost an average of 2.1 pounds over the 14 day period.

Magnesium Sulfate.—The magnesium sulfate appeared to give a more positive water balance but could not be compared with the control balances for sodium, potassium, or nitrogen because the values did not agree well for the first 5 day control period. The patient gained 2 pounds while receiving magnesium sulfate and had a net gain of 2 pounds for the 14 day period.

TABLE II. WEIGHT CHANGES IN POUNDS DURING CONTROL AND DIURETIC PERIODS

	INITIAL CONTROL PERIOD (5 DAYS)	DIURETIC PERIOD (5 DAYS)	FINAL CONTROL PERIOD (4 DAYS)	NET CHANGE
Control	−1.2	−0.9	+1.8	−0.3
Ammonium chloride 8.1 Gm. per day	−1.5	−3.2	+2.2	−2.5
Mercuhydrin 1 c.c. per day	−0.9	−1.0	+0.4	−1.5
Mercuhydrin 2 c.c. per day	−3.0	−3.3	+3.1	−3.2
Acid-ash diet	−1.4	−0.8	+0.1	−2.1
Magnesium sulfate 40 c.c. 50% per day	+1.0	+2.0	−1.0*	+2.0
Ammonium chloride 8.1 Gm. per day pre-eclamptic patients	−2.2	−5.6	+1.8†	−6.0

*Patient delivered after 13 days.
†Patients delivered after 11 days.

Comment

It is of clinical interest that therapeutic doses of ammonium chloride had greater diuretic effect in pregnant patients than did those of Mercuhydrin. Higher doses of Mercuhydrin might have been tested but it was noted that on 2 c.c. per day the blood urea nitrogen level of one patient rose from 28 to 42 mg. per cent. It remained constant in the other two patients. There is a possibility that mercurials might act synergistically with ammonium chloride in pregnant patients since they have been reported to do so in normal dogs.[6] Higher doses of ammonium chloride will probably not prove satisfactory. Brown and Bradbury[1] found that 12 or 16 Gm. per day substantially increased the incidence of nausea and vomiting.

Ammonium chloride is often given in an alternating schedule of 3 days on, 3 days off, 3 days on, etc. This practice takes advantage of the days of

greatest response to the drug. The results of this study suggest that when given for more than 5 consecutive days the drug would no longer have a diuretic effect, but that it might be used effectively for as long as 5 days. The fact that 8.1 Gm. per day of ammonium chloride in combination with a low-sodium diet did establish a negative sodium balance in both the normal and pre-eclamptic patients, even when considering the 4 day period of readjustment following therapy, testifies strongly to the clinical usefulness of such a regimen.

The diuretic response to the acid-ash diet was not as great as had been expected, considering that its potential acidity was equivalent to 28 c.c. of normal acid. This is equivalent to the amount of acid theoretically produced by 4.0 Gm. per day of ammonium chloride. However, virtually no diuretic response was obtained. Perhaps part of the explanation may lie in the concept that acidifying salts may act in the ultimate as osmotic diuretics with the distal secretion of ammonia entailing water for the excretion of whatever ammonium salts may be present in the urine.[7] The very high level of ammonium salts in the urine following ammonium chloride therapy is consistent with this hypothesis.

The effects of the diuretic agents (particularly ammonium chloride) on potassium excretion closely paralleled their effects on sodium excretion. However, the effect of ammonium chloride on potassium excretion in pre-eclamptic patients was less pronounced than that in normal patients, whereas the effect on sodium excretion was comparatively greater in the pre-eclamptic patients. No significance can be given to this, considering the limited number of pre-eclamptic patients studied.

It was noteworthy that in producing diuresis the agents used did not significantly alter nitrogen balance. Perhaps a diet of normal sodium content would give a positive nitrogen balance of greater magnitude than did the low-sodium diet, but such a comparison was not included in this study.

The term "balance" as used in this study obviously is not entirely correct since water was constantly being lost by respiration and insensible perspiration. Tests on most of the patients were made during a period when the temperature range in the hospital was 68-77° F. and the relative humidity 40 to 60 per cent. It was felt that the water lost by these patients was fairly constant in amount, and loss of electrolytes by sweating was at a minimum. The temperature and relative humidity ranges for the patients on the acid-ash diet were higher and may have partially masked the diuretic effects of the diet. Since the values for water balance were only relative and not absolute values, it was not considered necessary to estimate water of oxidation from the diets.

Conclusions

1. With the dosages employed, ammonium chloride had a greater diuretic effect than Mercuhydrin in pregnant patients, and in conjunction with a low-sodium diet maintained a negative sodium balance.

2. In pregnant patients, a low-sodium, acid-ash had little, if any, advantage as a diuretic agent as compared to a neutral-ash, low-sodium diet.

3. The effect of diuretic agents on excretion of several urinary constituents was roughly comparable to the effect on the balance of these constituents.

4. A similar but slightly greater diuretic response to ammonium chloride was achieved with pre-eclamptic patients as compared with normal pregnant patients.

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THE MERKEL MODIFICATION OF THE RICHARDSON TEST FOR THE DIAGNOSIS OF PREGNANCY

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IN APRIL, 1949, before the joint meeting of the Chicago, Kansas City, and St. Louis Gynecological Societies, a new chemical procedure for the diagnosis of pregnancy was presented. Prior to the appearance of this new technique in print, a colorimetric adaptation, devised by Merkel,[1] became available with details for the performance of the Richardson procedure.[2] Using the method as outlined in Merkel's article, we investigated this test in the hope that a practical, accurate, and rapid procedure for the diagnosis of pregnancy had been found.

Materials

All urine specimens examined were submitted, without history, by private physicians. As the Aschheim-Zondek test had been our standard pregnancy test, two consecutive morning urine specimens, specific gravity above 1.015, were available for the study on each patient in this series. Two months after the performance of the test, the physician was contacted and the results of the procedure verified. It was felt that this interval gave ample time for conclusive verification of the status of the patient and the accuracy of the result of the Merkel procedure. The figures presented in this study, therefore, indicate the accuracy of the procedure when testing specimens of urine from unknown patients whose clinical histories and findings suggest pregnancy but are not diagnostic.

Methods

The technique suggested by Merkel using the Leitz electrophotometer with a blue filter (wave length: 475 mμ) was followed, except for the following slight modifications: (1) It was found that vigorous shaking of the alkalinized urine with chloroform resulted in no clear separation between the two phases in any of the urine samples tested. This emulsion at the interface of the two liquids was compressed into a button by centrifuging for one minute at 2,000 r.p.m., allowing for complete removal of the aqueous phase by capillary pipette. (2) As the original procedure calls for various reagents in volumes measured in terms of drops, it was felt that standardization in terms of milliliters would obviate any differences that might result from different pipettes. Using ten standard 1.0 ml. pipettes, an average was obtained and the following values substituted as indicated: 4 drops N/2 sodium hydroxide to 0.3 ml.; 10 drops N/2 sulfuric acid to 0.7 ml.; 10 drops 0.1 per cent 2,4 dinitrophenylhydrazine reagent to 0.25 ml.

Pyruvic Acid.—The following modification of the method of Fister[3] for the measurement of pyruvic acid was adapted to the reagent values employed

in the Richardson procedure. To 4.0 ml. of urine in a Pyrex test tube, 0.3 ml. of N/2 sodium hydroxide is added and the alkalinized urine extracted by vigorous shaking with chloroform for one minute. To the aqueous phase, 0.7 ml. of N/2 sulfuric acid and 0.25 ml. of 2,4 dinitrophenylhydrazine are added and the mixture allowed to stand for twelve minutes.

Xylene, 5.0 ml., is then added and the 2,4 dinitrophenylhydrazones are extracted by shaking for one minute. The xylene phase is removed by capillary pipette and is extracted with 5.0 ml. of 10 per cent sodium carbonate, shaking vigorously for one-half minute. After removal of the xylene phase, the sodium carbonate extract is alkalinized with 2.0 ml. of N/2 sodium hydroxide. This is allowed to stand for two minutes for full color development.

The xylene portion of the extract following the removal of the pyruvic acid with sodium carbonate contains other 2,4 dinitrophenylhydrazones, a good portion of which appears to be that of estrone. These hydrazones may be demonstrated by evaporating to dryness with an air stream and dissolving the residue in 5.0 ml. of 95 per cent ethanol. The addition of 2.0 ml. of N/2 sodium hydroxide and allowing to stand for two minutes bring further color development.

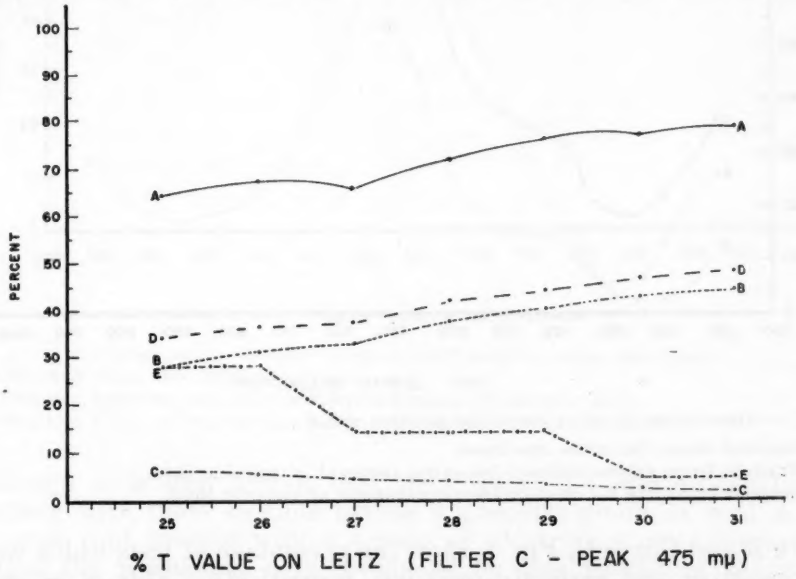

Fig. 1.—Per cent transmission value on Leitz (Filter C—peak 475 mμ).

A, Agreement between two consecutive morning urine samples, both samples reading above, below, or equal to the indicated transmission value.

B, Correct positive tests (percentage of total tests). Both samples reading equal to or below the indicated transmission values.

C, Correct negative tests (percentage of total tests). Both samples reading above the indicated transmission values.

D, Total correct positive and negative tests (percentage of total tests).

E, Negative tests with subsequent abortion. Both samples reading above the indicated transmission values (percentage of total abortions).

Results

This report is based upon 302 patients from whom two consecutive morning urine samples were obtained. All results in this series have been conclusively verified as indicated in the preceding paragraph. As it was obvious early in our studies that poor agreement was being obtained between the two urine samples from the same patients, results were interpreted using a greater number of transmission values than the 27 per cent suggested by Merkel. Agreement between the two specimens from the same patients ranged from 64.4 per cent

at 25 per cent transmission to 78.1 per cent when 31 per cent transmission was used as the critical value. At the 27 per cent transmission figure suggested by Merkel as the point of differentiation between positive and negative results, an agreement of 65.9 per cent was obtained. The results, therefore, of one-third of our entire series are incorrect in that they failed to be consistent on two consecutive mornings. Curve *A*, Fig. 1, indicates the percentage agreement between the two specimens from a single individual at the various transmission values used in this study.

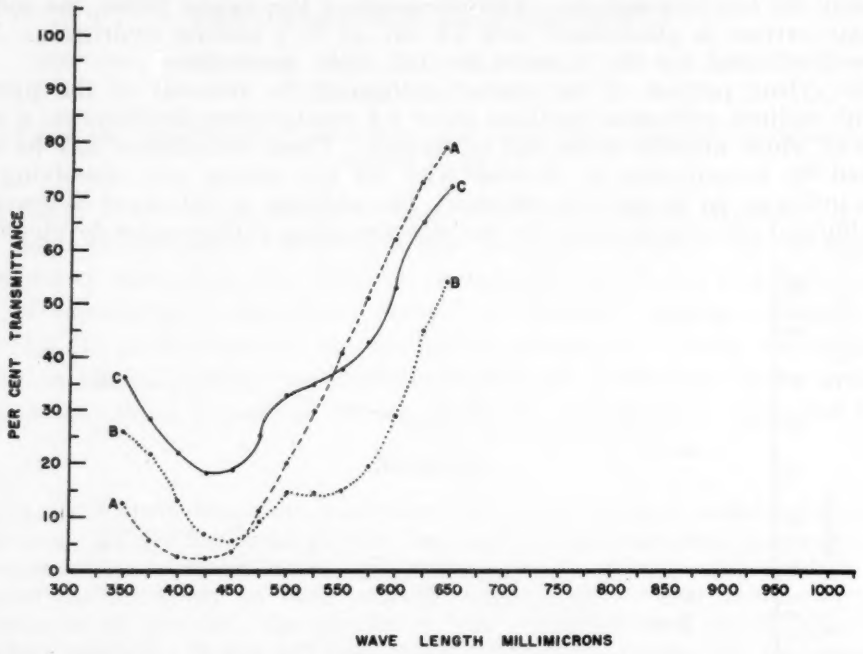

Fig. 2.—Absorption curve of correctly positive urine.

A, Obtained from the urine specimen.
B, Obtained from xylene extract following removal of pyruvic acid.
C, Obtained from the 2,4 dinitrophenylhydrazone of pyruvic acid.

Curve *B* and Curve *C*, Fig. 1, show the percentage of tests which were both correctly positive and correctly negative, respectively. This is expressed in terms of total accuracy of the procedure in the 302 patients tested in Curve *D*. This curve reveals that the over-all accuracy of the procedure in our hands is 37 per cent when 27 per cent transmision is used as the critical value. This figure improves slightly when 31 per cent transmission is used, as false negatives were found to be eliminated at a greater rate than additional false positives accumulated. Beyond the 31 per cent figure, false positives increase at a rate which negates any improvement in the accuracy figure by the elimination of false negative results.

Twenty-one patients of this series aborted some time subsequent to the completion of the test. Curve *E*, Fig. 1, shows that a negative test was obtained in only 14 per cent of the total number of patients aborting when using the 27 per cent transmission. At 25 per cent transmission, this figure improves to include 29 per cent of the total aborters.

Comment

Out of a total of 302 patients studied, only 195 showed agreement between their two urine samples. The cases in disagreement were classified as incorrect

results on the basis that no interpretation could be given in those cases in which a positive result was obtained one day and a negative result the next day. This factor, in conjunction with the false results obtained, has produced a total accuracy figure of 47 per cent when a transmission value of 31 per cent is used as the criterion of a positive response.

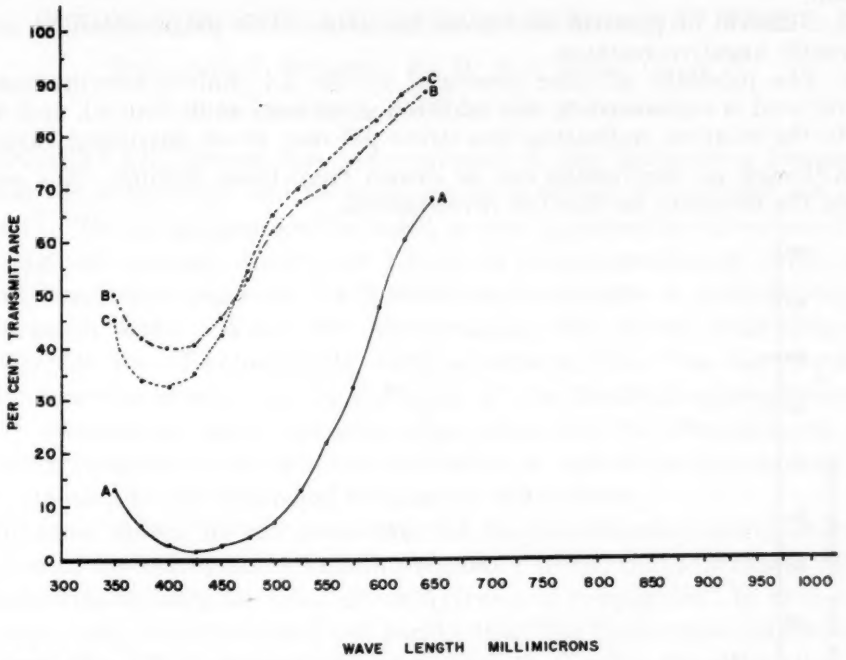

Fig. 3.—Absorption curve obtained from falsely positive urine specimens.
A, Obtained from the urine specimen.
B, Obtained from the 2,4 dinitrophenylhydrazone of pyruvic acid.
C, Obtained from xylene extract following removal of pyruvic acid.

Although it is well known that the reagent 2,4 dinitrophenylhydrazine will combine with those steroids having a phenolic group as well as simpler organic acids and phenols with a ketone or aldehyde group, Richardson has stated that the permanent color produced by this procedure is due to the hydrazone of free estrone. Pyruvic acid has been dismissed as a possible contributor to the color formed. We have determined the absorption curve for a urine specimen giving a true positive result (Curve *A*, Fig. 2). This curve bears little resemblance to those obtained for the 2,4 dinitrophenylhydrazine of free estrone* as obtained in this laboratory (Fig. 4) and reported by Merkel. However, the absorption curve for the 2,4 dinitrophenylhydrazones found in the xylene extract following the removal of the pyruvic acid (Curve *B*, Fig. 2) is comparable in all of its characteristics to that obtained from estrone. The absorption curve obtained from the sodium carbonate extract (Curve *C*, Fig. 2) appears to be contaminated with some estrone as its characteristics lie somewhere between that obtained for pure pyruvic acid and that of free estrone. Similar studies carried out on urine giving a false positive reaction yield a curve essentially similar to that found in the case of a true positive urine (Curve *A*, Fig. 3). The sodium carbonate and xylene extracts give no indication of the presence of the 2,4 dinitrophenylhydrazone of estrone. They do, however, nearly reproduce the curve for pyruvic acid.

*The authors wish to thank Ayerst, McKenna & Harrison, Ltd., for supplying free estrone for this work.

Although no program of intensive investigations has been carried out into the role of pyruvic acid, the following observations have been made during the course of our work:

1. Male urine frequently gives a transmission value of less than 27 per cent.
2. Nonpregnant females frequently give positive results following physical exertion.
3. Removal of pyruvic acid from the above false positive results produces a correctly negative reaction.
4. The intensity of color produced by the 2,4 dinitrophenylhydrazone of pyruvic acid is influenced by the addition of various acid, neutral, and alkaline salts to the solution, indicating that urine pH may be an important variable.

Although no conclusions can be drawn from these findings, they certainly suggest the necessity for further investigation.

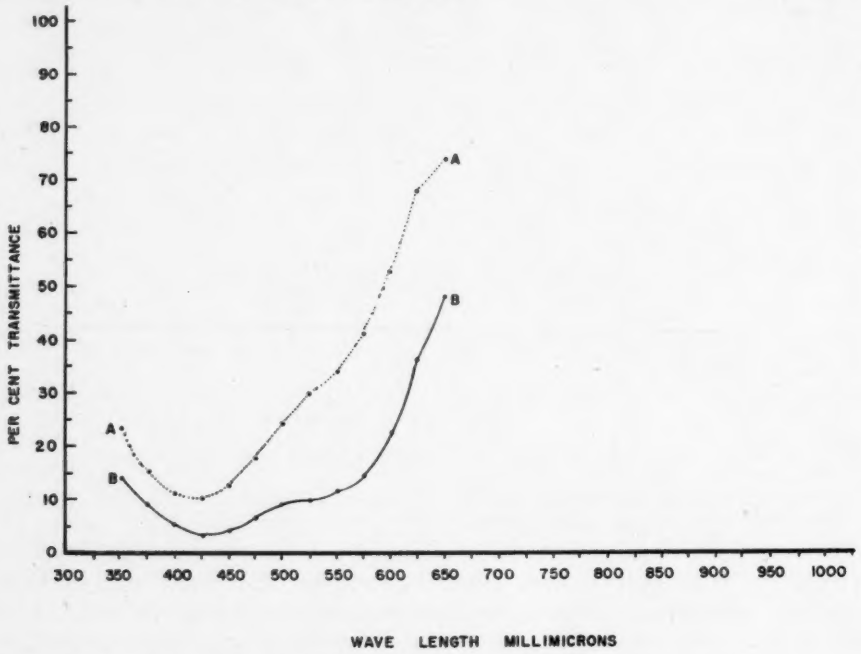

Fig. 4.—2,4 Dinitrophenylhydrazone absorption curves obtained from:
A, 1.15 mg. per cent pyruvic acid in distilled water.
B, 10.0 mg. per cent free estrone in ethanol.

Conclusion

In 302 patients with unknown histories, the Merkel modification of the Richardson procedure gave an over-all accuracy of 37.1 per cent in diagnosing pregnancy. Maximum accuracy using a transmission value of 31 per cent as the critical level was 47.3 per cent. Further studies indicate that urine pyruvic acid may enter into the permanent color formation. It seems unlikely that free estrone is the only contributor.

The authors wish to express their appreciation to Miss Jane Egan and Miss Martha Feldman for their technical assistance.

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CONCERNING THE RICHARDSON PREGNANCY TEST

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(From the Rees-Stealy Clinic Research Foundation)

WIDESPREAD interest has been evinced in the Richardson biochemical test for pregnancy[1] and its more recent extension to prenatal sex determination.[2] The pregnancy test is based on the colorimetric detection of free (unconjugated) estrone directly in 2.0 ml. of human pregnancy urine, using either of two ketone reagents, 2,4-dinitrophenylhydrazine or m-dinitrobenzene (Zimmermann test). While the Zimmermann test shows some degree of specificity for the 17-ketosteroids, such as estrone, since the test requires a methylene-ketone group, this is not true of the 2,4-dinitrophenylhydrazine method. Because we have had some experience with the Zimmermann color test and its relation to estrone determination in human pregnancy, we wish to call attention to our published findings on the subject.

We[3] have shown, by our procedure for the fractionation and photometric estimation of the estrogens in human pregnancy urine, that satisfactory Kober and Zimmermann tests for total estrone (free and conjugated) in acid-hydrolyzed urine may be anticipated not earlier than the tenth week following the last catamenia. We[4] subsequently reported that, with the utilization of a color correction equation for the Kober reagent, the estrogens in human urine with low estrogen content could be estimated by our procedure. At that time we reported two of a series of six tests on women's urine, collected one week after the last missed catamenia in normal pregnancy. In these and additional (unpublished) tests, we have demonstrated total estrone titers for human pregnancy urine collected during the first month following the missed catamenia, ranging from 40 to 200 micrograms per twenty-four hour specimen. This amount would be approximately 0.04 to 0.2 microgram per milliliter of urine. In our experience, the Zimmermann test produced no visible color even with pure solutions of estrone in this concentration range other than that yielded by the blank. The estrone could not, therefore, be detected directly in the urine.

We have recently studied the nature and extent of estrogen conjugation as reflected in human pregnancy urine. In the fifteen toluene-preserved urine specimens studied thus far,[5] there were never more than traces (less than 50 micrograms per twenty-four hour specimen) of free estrogens and only a fraction of these was the ketonic estrogen, estrone. Unpreserved urine specimens may show higher unconjugated estrone titers than those in toluene-preserved urine, but they should not exceed the 40 to 200 microgram total estrone level at the time when a pregnancy test would have some significance, i.e., one month after the last missed catamenia.

Although Richardson has purportedly taken advantage of the acidic nature of estrone to free it from interfering chromogens, a closer examination of his procedure reveals that this is not the case. Engel[6] has pointed out that all the estrone passes into the organic phase on distribution between ethyl ether and aqueous solution at a pH below 11.0. We have examined twelve urine specimens, chosen at random from our obstetrical service, which had pH values (Beckman pH meter model G) ranging from 5.5 to 7.6, with an average of 6.25. After alkalinization as described by Richardson (one drop of 0.5 normal sodium hydroxide solution per milliliter of urine), these specimens had pH values ranging from 6.5 to 10.0 with an average of 8.6. We have found (unpublished data) that estrone equilibrates between chloroform and M/20 sodium tetraborate solution, pH 9.2, in the ratio 19/1. Under the conditions of the Richardson test, therefore, we would expect to find the major fraction of any free estrone present in human pregnancy urine in the chloroform extract which he discarded. Following the chloroform extraction of unhydrolyzed urine, conjugated estrone remains in the aqueous phase along with conjugated neutral 17-ketosteroids (androgens) present in amounts approximately one hundred times that of the estrone. The estrone and the neutral 17-ketosteroids would be likely to react with both of the color reagents used in the Richardson test.

To overcome the obstacles mentioned, workers who are studying the steroids have had to resort to elaborate methods of hydrolysis, extraction, and fractionation in order to utilize color tests with limited specificity. We have not attempted to verify Richardson's reported production of a brown color with human pregnancy urine and 2,4-dinitrophenylhydrazine. Nevertheless, our data on free and total estrone titers in early human pregnancy urine indicate re-examination of the rationale of the Richardson biochemical test for pregnancy.

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VAGINAL DELIVERIES DURING PROFOUND CURARIZATION

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THE use of curare derivatives as adjuncts to anesthesia in obstetrics has been reported by Whitacre and Fisher[1] and others.[2-12] No instances of infant depression due to curarization have been reported with the therapeutic dosages employed, nor has the postpartum contractility of the uterus been reported as being adversely affected. Neuromuscular blocking of human fetal tissues by curarization has been demonstrated by Buller and Young.[13] Harroun, Beckert, and Fisher[14] reported normal reflex activity in a 4½ months fetus delivered after a thirty-five minute period of apnea in the mother during a curare-nitrous oxide anesthesia, and an uninhibited contractility of the postpartum uterus.

On the basis of reported observations the contention that curare does not pass the placental barrier has been widespread. However, it is difficult to accept this concept because of the known placental transmission of other water-soluble drugs and because placental transmission of d-tubocurarine chloride from fetus to mother has been reported in rabbits.[13]

Our interest in the use of d-tubocurarine chloride for obstetrical purposes centered on the question of placental transmission of the drug. The purpose of this study was twofold: to observe the clinical effects of d-tubocurarine chloride on infants delivered of profoundly curarized mothers, and to make chemical analyses of the curare content of cord bloods from these infants. Blank values were to be obtained in similar analyses of cord bloods from infants delivered of noncurarized mothers for comparison.

Experimental

Six mothers in labor at term were selected for the curarization study. Five other mothers in labor at term were used as controls. Selection was on the basis of freedom from serious antepartum complications and lack of interfering premedication. This latter consideration was important in view of the nonspecificity of the analytical procedure of Quinn and Woislawski.[15] The precautions necessary in the clinical application of the procedure for the determination of d-tubocurarine chloride in human plasma after intravenous injection during anesthesia were pointed out by Pittinger and associates.[16]

Adequate precautions were taken to insure the safety of the mothers and infants. Two anesthesiologists, prepared to attend to the respiratory needs of mother and child, were present during each delivery of the curarized moth-

ers. The obstetrician was prepared if necessary to deliver the infant with low forceps which was done in two instances because of the weak expulsive force of the mothers. d-Tubocurarine chloride was withheld until the cervix was completely dilated and the head of the infant well down on the perineal floor. A commercial preparation of the drug containing 3 mg. per milliliter was then injected into an antecubital vein after the mother had breathed an 80:20 mixture of nitrous oxide-oxygen for several minutes. The total doses of d-tubocurarine chloride ranged from 21 to 60 mg. (Table I). These large doses were deliberately used in an effort to obtain clinical and chemical evidence of placental transmission of the drug. Adequate ventilation was provided by means of a mask and rebreathing bag; endotracheal intubation was performed in one case to facilitate the maintenance of a satisfactory airway. After resumption of spontneous respirations, the latter were assisted until they were considered adequate. Tensilon, a curare antagonist, was administered intravenously in some cases to shorten the period of recovery from curarization, but not until after the blood samples had been drawn from the mothers and the cords for d-tubocurarine chloride analysis.

Two samples of blood were drawn from the curarized mothers, one for the determination of the blank prior to curarization, and the other for the determination of the plasma concentration of the drug at the time the cords were clamped. The cord blood samples were taken immediately after clamping. It was the opinion of the attending obstetrician in each case that the placenta was still attached when the cord was clamped.

Observations

Table I contains the data pertaining to the age and parity of the mothers and the drugs administered to them as premedication for delivery. Mothers A to F were curarized; mothers G to K were noncurarized controls. It is evident that the elapsed time between administration of d-tubocurarine chloride to the mothers and the drawing of blood samples for analysis ranged from minutes to over an hour and a quarter. It is believed that adequate time was allowed for placental transmission of the drug.

It was our clinical impression that the profound states of curarization depressed the frequency and strength of the uterine contractions and perhaps contributed toward the necessity for the forceps delivery in the instances of mothers E and F. There was no evidence of uterine atony in the curarized patients and the uterine response to ergonovine maleate was excellent.

Five of the six infants delivered of curarized mothers cried spontaneously shortly after delivery. Spontaneous respirations were delayed two to three minutes in the infant delivered of mother F. Curarization of the infant was not believed to be responsible for this delay since respiratory and other muscular activity did not seem embarrassed after it began.

Table II shows the plasma concentration of d-tubocurarine chloride as determined by chemical analyses of maternal and cord blood taken immediately after the cords were clamped. The plasma concentrations of d-tubocurarine chloride in the mothers at the time the cords were clamped ranged from 1.9 to 8.2 gamma per milliliter. These values are typical of those previously reported[16] for a series of patients deeply curarized during anesthesia for surgical procedures. These values were determined analytically with consideration of the "blank" value obtained for the mothers' blood drawn just prior to curarization.

In the case of the infants, cord blood samples for "blank" determinations prior to curarization of the mothers obviously were unattainable. Hence, in Table II, the cord plasma "equivalents" of d-tubocurarine chloride for the

infants delivered of the curarized mothers include the "blank" value as well as any actual drug present; for the infants delivered of the noncurarized mothers, these values represent "blanks" only. The cord blood "equivalent" for the infant delivered of mother D was not obtained because of technical difficulties associated with its determination. If the average value of 1.0 obtained for the cord blood "blanks" of the noncurarized cases is subtracted from the average value of 1.1 obtained for the cord plasma samples of the five curarized cases considered, a difference of only 0.1 gamma is obtained. This difference is not statistically significant, and hence no positive laboratory evidence was obtained to indicate the presence of d-tubocurarine chloride in the cord bloods of the infants delivered of the curarized mothers.

TABLE I. PREMEDICATION, ANESTHETIC, AND CURARIZATION DRUGS ADMINISTERED TO THE MOTHERS

MOTHER	AGE (YEARS)	PARITY	PREMEDICATION DRUG, DOSAGE, AND ANTEPARTUM TIME OF ADMINISTRATION	ANESTHETIC AGENTS	d-TUBOCURARINE CHLORIDE DOSE (MG.)	ELAPSED TIME IN MINUTES BETWEEN d-TUBO. AND DRAWING OF BLOOD SAMPLES
A	26	i	Demerol 100 mg., I.M.; 5¾ hours	N_2O-curare	15	2-3
B	28	iii	None	N_2O-curare	24	5-6
C	20	ii	None	N_2O-curare	9	34-35
					21	23-24
D	22	i	Nembutal 100 mg. per os; 9 hours	N_2O-curare	6	77-78
					15 (subcutaneous?)	77-78
					30	5-6
E	36	viii	None	N_2O-curare	30	9-10
F	39	xii	None	N_2O-curare	30	15-16
					15	12-13
					15	11-12
G	16	i	Demerol 50 mg., I.M.; 3 hours, 50 minutes	N_2O	0	--
H	30	vii	None	Procaine 1 per cent local	0	--
I	21	i	None	N_2O	0	--
J	35	v	None	N_2O	0	--
K	20	iii	None	N_2O	0	--

TABLE II. PLASMA CONCENTRATIONS OF d-TUBOCURARINE CHLORIDE AT TIME OF CLAMPING CORDS

MOTHER	d-TUBOCURARINE CHLORIDE (GAMMA/C.C. OF PLASMA)		AVERAGE "EQUIVALENTS" OF d-TUBO. IN CORD PLASMA
	MOTHER	CORD PLASMA "EQUIVALENTS" OF d-TUBO.	
A	3.3	0.9	
B	8.2	0.6	
C	7.0	1.3	
D	5.6	?	1.1
E	1.9	1.2	
F	3.1	1.3	
G	--	1.4 (blank)	
H	--	1.4 (blank)	
I	--	1.5 (blank)	1.0
J	--	0.3 (blank)	
K	--	0.4 (blank)	

Although not a part of this study, in more than a dozen cesarean sections done with only nitrous oxide-curare anesthesia in which the mothers were deeply curarized, there were no instances of infant depression attributable to curarization.

The results of these findings may be interpreted by some to support the contention that d-tubocurarine chloride is not transmitted by the placenta from mother to fetus. However, in view of the known rapid rate of decline in the plasma concentration of the drug after intravenous injection during anesthesia,[16] we believe that the relatively small amount which probably does pass to the fetus likewise rapidly disappears from the fetal plasma, leaving a residual concentration too low for detection by the method of analysis employed.

Since the completion of this study on human beings, placental transmission of d-tubocurarine chloride from mother to fetus has been proved unequivocally in dogs[17] by the injection of the drug into one of the uterine arteries. The reason for intra-arterial administration of large doses of d-tubocurarine chloride was to provide a plasma level of the drug at the placenta such that the amounts transmitted to the fetuses would be detectable by chemical analysis. The dosages used when compared on a weight basis represent five to ten times the amounts which ordinarily might be given clinically. Pups with intact fetal circulation were curarized; litter mates whose circulatory pathways with the mother had been interrupted prior to the injection of the drug were not curarized. A composite movie was prepared demonstrating this phenomenon in several dogs. Chemical analyses performed on the plasma of the delivered pups corroborated the presence of d-tubocurarine chloride.

Conclusions

We have confirmed the impression that for practical purposes no significant quantities of d-tubocurarine chloride will reach the baby of a mother curarized by the usual intravenous injection of a therapeutic dose of the drug.

Profound curarization of mothers during the second stage of labor seems to diminish the frequency and force of uterine contractions.

Curarization of any patient is safe only when done by a person familiar with the effects of the drug employed and competent in the management of the respiratory problems which may arise.

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THE USE OF DIENESTROL TO INHIBIT LACTATION IN NONNURSING MOTHERS*

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IN A population where a very appreciable percentage of postpartum women either cannot or do not desire to nurse their babies, obstetricians have been interested in finding a way to prevent the breast engorgement and lactation which so frequently occur in these patients. For a number of years, various different hormones have been used in attempts to prevent this normal physiological activity of the postpartum period and, although estrogens of various types and androgens have been found to be satisfactory under certain circumstances, they are likely to have very undesirable side effects. The rationale for the use of sex steroids for the purpose of the suppression of lactation is somewhat devious. The sudden lowering of the blood estrogen titer and concomitant lactation which follow parturition have led to the belief that possibly the high estrogen level which occurs during pregnancy has some inhibitory effect on the pituitary gland which prevents it from secreting lactogenic hormone.[1] This is notwithstanding the fact that lactogenic hormone and luteotrophic hormone are probably the same substance and that possibly there is a fairly high concentration of this hormone in the individual throughout pregnancy. Regardless of this, however, it is considered that following parturition the estrogen inhibitory influence on the pituitary gland is removed and the lactogenic hormone is secreted and/or liberated and lactation results. The obvious therapeutic implication of this theory, therefore, is that the administration of large amounts of estrogen will again suppress pituitary activity and therefore suppress lactation. Interestingly enough, this frequently is the case.

However, there is no question but that there must be a neurohumoral mechanism involved in this process in addition to one of pure pituitary stimulation. There are, for instance, apparently well-authenticated cases described in the literature[2] where the stimulation of repeated suckling has resulted in lactation in women who are not, nor have been, pregnant. The suckling of baby infants is actually the responsibility of grandmothers in certain African tribes and this interesting socioanthropological custom has been reported as even occurring in this country.[3] In certain instances milk production has been stimulated in nulliparous women by persistent suckling.[2] There is no

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question, therefore, but that pregnancy is not necessary as a precursor to lactation. Galactorrhea is not infrequently present in acromegaly and in other abnormally produced changes in hormonal mechanism such as surgical removal of the ovaries.

In this connection it is interesting to note that many years ago a syndrome was described in which amenorrhea and lactation persisted sometimes for many years following parturition, even though, apparently, there was no stimulation which might have induced this persistent condition. This was probably described first by Chiari[4] in 1855 and by Frommel[5] in 1882 and has been redescribed with variations for many years. There are no adequate theories as to why this syndrome actually occurs but it apparently has some connection with abnormal pituitary and ovarian activity.

The persistent thought, however, that suppression of pituitary activity might lead to suppression of lactation has resulted in numerous clinical investigations especially over the last ten or fifteen years concerning the action of either natural or synthetic estrogens during the postpartum period for this purpose.

The clinical attitude concerning this procedure has been well summarized by Morton and Miller[6] who, in 1951, treated 234 postpartum women with diethylstilbestrol. Although, in reviewing the past literature, they found numerous rather equivocal results, their own conclusion was that 90 per cent of the patients treated had a very satisfactory prevention of lactation. However, they are not in agreement with other clinical investigators when they state that there were practically no complications in connection with this treatment. It has been a not infrequent experience to find that after cessation of estrogen therapy occasional patients have severe and pronounced uterine bleeding, apparently as a symptom of estrogen withdrawal. This is represented by a sudden increase in lochia. Also, occasionally at this time, the breasts become engorged and lactation begins, so that the symptom for which medication was given is merely postponed and not prevented. For this reason other substitutes were searched for which would produce the desired effect without the attendant complications and androgens were tried. There have been numerous reports of this type of therapy in the literature, two of which, those of Kurzrock and O'Connell,[7] and Lass,[8] are from the Sloane Hospital for Women, and are therefore compatible in terms of clinical material and control with the present series. Kurzrock and O'Connell, using testosterone proprionate, and Lass, using methyltestosterone, obtained excellent results with the use of androgens and do not describe any undesirable aftereffects or complications.

The difference, however, between the use of sex steroid therapy and only symptomatic therapy has not been sufficiently radical so that the continuation of steroid therapy has been advisable. Apparently the advantages of steroid therapy have not been sufficiently greater than the advantages of no treatment, or merely symptomatic treatment, to make the bother of giving these steroid medications worth while and, therefore, on both the Ward and Private Services of the Sloane Hospital for Women the use of sex steroids for the pur-

poses of suppression of lactation has been largely given up. At the present time no other treatment is being used than supporting breast binders and analgesics, if necessary, plus fluid restriction and occasional ice caps.

In 1948 Dunlop and Diddle[9] treated 374 puerperal mothers with another type of estrogen known as dienestrol in order to compare the effects of this estrogen with alpha-estradiol and diethylstilbestrol. These writers were under the impression that breast engorgement and subsequent lactation did not occur following the discontinuation of dienestrol as it did with stilbestrol and estradiol, nor did they find any increase in lochia or evidence of withdrawal bleeding following the cessation of dienestrol therapy.

These writers pointed out that there was a distinct difference between breast engorgement and lactation and thought that these two symptoms were apparently independent of one another. Their attitude was that engorgement was caused by lymphatic and vascular stasis and not by distention of milk ducts. They were also of the opinion that prevention of lactation could not be carried out if any mechanical stimulus such as suckling or breast massage was used in attempts to empty the breast. Any mechanical stimulus produced a continuation of lactation even during the administration of any of the substances given to suppress it.

In order to study further the effect of dienestrol on inhibition of lactation the following clinical experiment was carried out.

Materials and Methods

A total of 160 patients were used in this study. These patients were all taken from the Ward Service of the Sloane Hospital for Women. All patients had stated that they did not desire to nurse. No multiparous patients were included who previously on conservative treatment had failed to lactate. Dienestrol* was the synthetic estrogen used throughout the study. In all cases when it was used the drug was started within 24 hours following delivery.

Observations of the patient's status were made daily during the hospital stay which averaged six days. In addition, the patients receiving dienestrol were all seen approximately 48 hours following the cessation of therapy at which time an endometrial biopsy was taken. This procedure was done to ascertain any possible effect of dienestrol on this end organ. Finally an attempt was made to see all of the patients at the first postpartum visit, which at our hospital is at six weeks. About 50 per cent of the women were seen at this time. Contact was made with the remainder by telephone or letter.

Five groups of patients were studied. Originally it was planned to study one group receiving dienestrol of a certain dosage and compare it with a control group. Because of the number of failures in preventing lactation with the first dosage used, it was decided to increase the dosage gradually until there were finally four dosage groups in the series, and one control group.

Group A.—Twenty-one patients were given dienestrol, 0.5 mg. twice daily for three days, followed by 0.5 mg. daily for seven days.

Total = 6.5 mg. in 10 days.

Group B.—Twenty-two patients were given dienestrol, 1.5 mg. twice daily for three days; then 1 mg. daily for three days; followed by 0.5 mg. daily for three days.

*Supplied through the courtesy of White Laboratories, Inc.

Total = 13.5 mg. in 9 days.

Group C.—Twenty patients were given dienestrol, 2.5 mg. twice daily for three days; then 1.5 mg. twice daily for three days; then 0.5 mg. twice daily for three days; followed by 0.5 mg. daily for three days.

Total = 28.5 mg. in 12 days.

Group D.—Twenty-two patients were given dienestrol, 10 mg. daily for five days; then 2.5 mg. twice daily for two days; then 1 mg. daily for two days; followed by 0.5 mg. daily for two days.

Total = 63 mg. in 11 days.

Group E.—Seventy-five patients received no drugs except codeine and aspirin when needed.

A gradually decreasing dosage level in all categories was used because it was thought that this technique might decrease the possibility of withdrawal bleeding.

TABLE I. RESULTS

GROUP	NO. OF PATIENTS	INHIBITION OF LACTATION			PAIN OR ENGORGEMENT		
		EXCELLENT	FAIR	POOR	EXCELLENT	FAIR	POOR
A 6.5 mg./10 d.	21	4	5	12	14	6	1
B 13.5 mg./ 9 d.	22	4	2	16	16	6	0
C 28.5 mg./12 d.	20	3	8	9	15	3	2
D 63. mg./11 d.	22	0	2	20	11	10	1
Total	85	11	17	57	56	25	4
E Controls	75	34	29	12	40	30	5

TABLE II. COMPARISON OF RESULTS

		DIENESTROL 85 CASES	CONTROLS 75 CASES
Not lactating at any time		11	49
Lactating when leaving hospital		53	3
Lactating 6 or more days		57	0
Patients seen 6 weeks post partum		29	
Lactating at 6 weeks		15	
Lactating spontaneously		10	
Lactating on pressure only		5	
Not lactating at 6 weeks		14	
Withdrawal lactation occurred in	5		
On Plan B	1		
On Plan C	1		
On Plan D	3		

Results

The results are shown in Tables I and II.

Results were called "excellent" if there was no lactation and if there were no pain and engorgement.

Results were called "fair" if lactation was less than 48 hours and if pain and engorgement were slight, requiring no analgesics.

Results were called "poor" if lactation persisted for more than 48 hours and if pain and engorgement required analgesics.

The endometrial biopsies in practically all cases showed inactive proliferative endometrium. In a few cases from Group D an early estrogen effect was noted. No cases of withdrawal bleeding occurred.

No side effects such as nausea, vomiting, dizziness, etc., were reported from the patients taking dienestrol.

Comment

The results of this study indicate that dienestrol does not inhibit lactation; on the contrary it appears to prolong the period of lactation. The relief which dienestrol provides in elimination of painful and engorged breasts is about the same as that in the control group. This symptom occurred in only a small percentage of either group.

The study of the endometrial biopsies confirms the belief of Rakoff[10] that dienestrol has little effect on this end organ at this early postpartum period.

Summary

1. Dienestrol was given to 85 nonnursing mothers in varying dosages for the purpose of inhibiting lactation.

2. Lactation was completely inhibited in only 11 patients (13 per cent).

3. In a control group of 75 patients receiving no estrogens, lactation was completely inhibited in 49 patients (65 per cent) by symptomatic therapy.

4. The suppression of breast engorgement and pain was about the same in treated and untreated patients.

5. Dienestrol appears to have little effect upon the endometrium of the early postpartum patient. No case of postpartum bleeding was recorded. No side effects were noted.

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Rh ISOSENSITIZATION, INTRAUTERINE FETAL DEATH, AND HYPOFIBRINOGENEMIA

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COAGULATION defects due to absence or decrease in the fibrinogen content of the blood have been described in cases of hemorrhagic shock,[1] in certain severe cases of hemorrhage due to abruptio placentae,[2] in amniotic fluid embolism,[3] and in Rh-isosensitized women with dead fetuses in utero.[4, 5]

Weiner and his co-workers[4] were the first to call attention to this condition in Rh-isosensitized women carrying dead fetuses, a case having been observed at the Boston Lying-in Hospital in 1946. This patient had ecchymotic areas of the skin, intrapartum and postpartum hemorrhage; and, although no studies of the blood coagulation were done, multiple transfusions brought about her recovery. This suggested further investigation and, out of fifteen cases of Rh-isosensitized women with dead fetuses in utero in the two years prior to Weiner's report, three were found to present marked coagulation defects.

The most recent report is that of Ratnoff and associates.[5] This patient was Rh isosensitized and carried a dead fetus for several weeks, going past calculated term. Fibrinogen was given and numerous fibrinogen determinations were made. Ultimately hysterectomy was necessary after adequate preparation with fibrinogen, as in the first case reported by Weiner.

Fibrinogen used in the treatment of these cases is supplied by the American National Red Cross. It is processed from blood collected from voluntary donors and is now being treated with nitrogen mustard which is subsequently neutralized, obviating the danger of homologous serum jaundice. The process is extremely costly and there is as yet no commercially obtainable product. It is therefore required that blood specimens be drawn before and after administration and sent to Dr. A. E. Weiner* for fibrinogen determinations, and that all clinical data be sent with them.

Methods of determining fibrinogen levels are discussed and technical details given in Weiner's reports[2] and in the report of Ratnoff's group in Cleveland.[5, 6] For practical purposes in the management of these cases a simple clot dissolution test is sufficient to establish the absence or diminution of the fibrinogen content of the blood. To determine this, 5 c.c. of venous blood is drawn into a serology tube and incubated at 37° C. Periodic inspection of the clot for degree of lysis is made for one hour. Complete dissolution indicates afibrinogenemia. Partial dissolution indicates hypofibrinogenemia. In the fibrinogen determinations

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reported by Ratnoff,[5] a normal fibrinogen level in nonpregnant human beings is given as 294 mg. per 100 ml. with a standard deviation of 60.3 and a standard error of 16.1.

Three cases are herewith added to those already reported in the literature.

Case Reports

Mrs. J. H. was a 21-year-old gravida ii, para i, whose expected date of confinement was Oct. 18, 1951. Her past history is of interest since in 1938, at the age of 9, she was hospitalized because of bronchopneumonia. The course was stormy. Pediatric consultation was obtained with the recommendation that the patient be given small blood transfusions. The blood was determined to be type 0 and two transfusions of 250 c.c. citrated blood were administered on two successive days. The patient improved and was discharged from the hospital in good condition. Careful study of the patient's chart reveals no evidence of transfusion reaction either time.

The patient was first seen on March 7, 1950. She was about six weeks pregnant, the estimated date of confinement being Oct. 29, 1950. The blood type was 0, Rh negative. The husband's blood was type B, Rh positive. On September 6, when the patient was 7 plus months pregnant, anti-Rh agglutinins were present in a dilution of 1:4 (Diamond). Further blood studies were as follows:

Sept. 23, 1950, anti-Rh agglutinins positive 1:8
Oct. 7, 1950, anti-Rh agglutinins positive 1:32
Oct. 14, 1950, anti-Rh agglutinins positive 1:64
Oct. 28, 1950, anti-Rh agglutinins positive 1:32

On Nov. 2, 1950, the patient was admited in labor and following a normal course of 13 hours, 18 minutes, was delivered by prophylactic forceps of a living female infant weighing 3,475 grams. The child's blood gave a positive Coombs' test and she received a replacement transfusion following which her course was uneventful and she is alive and well at this date. Following delivery the fundus uteri contracted well and there was no undue bleeding, total blood loss being estimated at approximately 100 c.c.

The patient was seen again on March 8, 1951, two months pregnant, the estimated date of confinement being Oct. 18, 1951. Once more the blood developed a high anti-Rh titer which eventually reached 1:256. The pregnancy, however, progressed in an apparently normal fashion until July 24 (28 weeks) when fetal death in utero occurred. The fetal heart was not heard; x-ray on August 20 was positive for fetal death.

On Sept. 8, 1951, approximately six weeks after fetal death, the patient was admitted to the hospital because of sudden profuse vaginal bleeding. When admitted, bleeding was slight but it was obvious that she had lost considerable blood. Preparations for transfusion were made. The patient went into labor and one and one-half hours after admission a macerated fetus, 28 cm. in length and weighing about 500 grams, was delivered. The placenta was immediately expressed intact.

From this time on, although the fundus remained relatively firm and despite the administration of Pitocin and Ergotrate there was steady vaginal bleeding. A transfusion of 1,500 c.c. of type 0 negative bank blood was administered. The patient's blood clotted within five to ten minutes but after a half hour's incubation was completely liquefied. Fresh blood was now obtained and an additional 2,000 c.c. was given. At 7 A.M., September 9 (9 hours after delivery), bleeding rather suddenly slackened and became approximately normal. The clot still completely liquefied on incubation and continued to do so until 18 hours after delivery when only partial liquefaction was observed. This became less but slight clot liquefaction on incubation was noted as much as 36 hours after delivery. Throughout the first week of the puerperium the lochia was a little profuse but the remainder of the puerperium was uneventful and at the time of her examination six weeks post partum the hematocrit was 40.

The second case is that of Mrs. S. She was a 28-year-old white gravida vi, Rh negative. Her first pregnancy resulted in a normal, full-term delivery in 1942. The second child, born in July, 1943, died on the third day, of erythroblastosis. In 1944 her husband was found

to be Rh positive, group 0, "heterozygous." The patient showed a small amount of anti-Rh agglutinins in the last month of her third pregnancy, August, 1944. Labor was induced prematurely. The placenta showed evidence of erythroblastosis. This baby was saved by blood transfusion. Her fourth pregnancy began in February, 1946; and in July, 1946, she showed anti-Rh agglutinins of hyperimmune variety, 1:64. A recheck of her husband's blood at this time showed him to be $Rh_2 = Rh_0$, and there was a question of homozygosity. The patient's agglutinins were reduced in October, 1946; and in November, 1946, she delivered a stillborn infant. One month post partum her blood showed a titer of 1:16. The fifth pregnancy resulted in a miscarriage in October, 1947. A transfusion was given at this time.

She was admitted to Hartford Hospital on Aug. 31, 1948, with the complaint of grossly bloody urine. Her last menstrual period was in December, 1947. She had not felt life since May, 1948, about 15 weeks prior to admission. At cystoscopy blood clots were seen coming from the right ureter, but no cause for this hemorrhage could be found. The skin showed numerous areas of ecchymosis, especially over the extremities. A few days prior to admission she had received penicillin injections for a sore throat, and there were large ecchymotic areas at the injection sites over the buttocks. She was given vitamin K.

On the third hospital day she began to bleed vaginally, and passed a macerated fetus, apparently intact with placenta and membranes. This fetus was estimated to have reached about 5 months' gestation, and to have been dead in utero about 4 months. Although the miscarriage appeared to have been complete she continued to bleed very profusely. Ergotrate, gr. 1/320, given intravenously, had no effect on the bleeding. Profuse bleeding continued. The patient went rapidly into shock. The blood pressure was 80/50. A transfusion of 500 c.c. of Rh-negative, type 0 whole blood was given, and the patient was immediately taken to the operating room where the uterine cavity was thoroughly explored, no retained tissue being obtained. Ergotrate, gr. 1/320, was again given intravenously. A second transfusion of 500 c.c. Rh-negative, type 0 blood was given during this operation. Several squares of Oxycel and a uterine and vaginal pack were inserted, and the hemorrhage seemed to be controlled. However, within 30 minutes she was bleeding profusely through the packs, and had again gone into shock. The blood pressure was 84/66. A third transfusion was then given. It seemed then that the only way left to control the bleeding was by hysterectomy. Therefore an emergency supravaginal hysterectomy was done, as quickly as possible after removal of the packs. A fourth and fifth transfusion were given during this procedure. The operation was done in 45 minutes. Recovery from shock was prompt and there was no bleeding from the wound or from any other source.

Convalescence was rapid. The course was moderately febrile. The maximum temperature was 103° F. (mouth). She was thought by the urologist to have a mild cystitis. She was recystoscoped on the seventh day following hysterectomy, at which time the urine was clear and there was no further bleeding from the right kidney. Slight angulation of the left ureter was noted at this time, but an intravenous pyelogram showed a normally functioning urinary tract.

She was discharged, improved, on the thirteenth hospital day, the tenth postoperative day.

Blood and laboratory studies were as follows:

Anti-Rh agglutinins were slightly positive, the titer not determined. Blood sedimentation rate was 3 mm. in 1 hour, checked twice. Blood fragility test was normal, hemolysis beginning at .50 and complete at .30. Toluidine blue test was negative for hyperheparinization. Blood serologic test was negative for syphilis. Total blood protein on the sixth postoperative day was 6.4 Gm. per cent, albumin 3.8, globulin 2.6, and albumin-globulin ratio 1:4. Blood smear two days preoperatively showed polymorphonuclear leukocytes 68, metamyelocytes 1, band forms 14, eosinophils 1, basophils 1, lymphocytes 26, monocytes 4, rare basophilia, hypochromasia plus, and anisocytosis plus. A smear taken just prior to operation showed: polymorphonuclear leukocytes 70, metamyelocytes 1, nonsegmented forms 5, eosinophil 1, lymphocytes 29, and slight hypochromasia.

Blood specimens drawn from the patient on the third and fourth hospital days were incubated two and three days at 37° C. and then examined, showing the following: (1) Blood showed a very small soft clot. (2) Serum plus normal clot showed no lysis. (3)

Clot plus normal serum showed no change. (4) Clot (from the prothrombin test of September 2) plus the patient's serum showed a small clot without change. (5) Clot (from the prothrombin tests of September 3 and 4) plus the patient's serum showed a fairly large and firm clot.

The most significant of all the blood studies was shown in a serology tube of blood taken on September 3, the day of her late miscarriage, severe hemorrhages, and operation. This blood clotted in about 3 minutes; it then reliquefied. A small, soft clot, about one-tenth normal size remained. This clot shrank down and did not become firm.

A summary of all other laboratory studies is shown in Table I.

Pathological examination showed a 340 gram, 18 cm. (crown-to-rump) macerated fetus, and a placenta, 12 cm. in diameter, weighing 260 grams. There was complete disappearance of the normal architecture of the fetal liver, indicating that intrauterine fetal death had occurred some time previously. Near one cornu of the removed uterus the inner surface was covered with a hemorrhagic-appearing tissue. The placenta showed extensive degenerative changes of the chorionic villi with a superimposed acute inflammatory reaction.

Examination of the patient six weeks postoperatively showed a clean cervical stump remaining. All ecchymotic areas of the skin had disappeared and there had been no new areas, no further hematuria, nor any other hemorrhage or evidence of blood dyscrasia. The patient felt well.

Complete recheck of all blood studies several months postoperatively showed them all to be normal.

The third case is that of Mrs. M., a 26-year-old white gravida iii, para ii, Rh negative. Five months before the beginning of her third pregnancy she sought advice as to whether or not to become pregnant again, her concern being over the loss of her second baby due to erythroblastosis. Her first pregnancy resulted in term delivery of a normal, 6 pound, 9 ounce, female infant in breech presentation, on Sept. 24, 1946. Her second pregnancy resulted in term delivery, spontaneously, of a stillborn female infant weighing 7 pounds, 4 ounces, on Nov. 15, 1949. No data concerning Rh are available other than that she was Rh negative and showed a "high titer" of anti-Rh agglutinins at this time. The husband and the 5-year-old daughter were found to be Rh positive. The patient's blood was reported to be negative for anti-Rh agglutinins on Sept. 13, 1951; and the patient was advised to try another pregnancy.

She reported for prenatal care on Feb. 6, 1952. Her last menstrual period was Dec. 4, 1951. The expected date of confinement was Sept. 11, 1952. The estimated duration of pregnancy was eight weeks. She had had some slight spotting which had turned brownish. There were no other significant positive findings in her past history or the history of her present pregnancy. She had a normal gynecoid pelvis. Her weight before pregnancy was about 114 pounds. Her ideal weight was 128 pounds. On Feb. 6, 1952, her weight was 119½ pounds, blood pressure, 114/76, hemoglobin 85 per cent. Blood serologic test was negative for syphilis. The urine was negative for albumin and sugar. The remainder of the physical examination was normal. This information and a specimen of the patient's blood were sent to Dr. L. K. Diamond at the Blood Grouping Laboratory in Boston. Dr. Diamond reported on Feb. 29, 1952, that the patient (1) was Group A, Rh negative; (2) showed a positive titer of anti-Rh agglutinins of 1:64 or possibly 1:128 against the C and D factors of the Rh complex; and (3) that there was possibly still another antibody against some of the less common blood group factors. He also stated that in view of the history and present findings there would be considerable doubt as to the nonexistence of any antibodies less than six months previously, when she first sought advice.

The husband's blood showed: (1) Group A, Rh positive, subtype R, definitely homozygous; and (2) genotype CDe/CDe.

The patient felt life about March 25, 1952. On April 30, 1952, the fundus was one fingerbreadth above the umbilicus, position right occipitoanterior. The fetal heart was heard in the right lower quadrant. On May 12, 1952, at approximately twenty-two to twenty-three weeks of gestation, the patient stopped feeling fetal movements. On May 26, 1952, the fetal heart could not be heard.

TABLE I

DATE	PROTHROMBIN	TOURNIQUET TEST	COAGULATION TIME	BLEEDING TIME	PLATELETS	HEMATOCRIT	HEMOGLOBIN	WHITE BLOOD COUNT
8/31	—	30 petechiae in 5 mins.	—	—	—	—	—	—
9/1	—	—	40 minutes* no clot retraction	1 minute, 25 seconds 1 minute, 30 seconds (2 P.M.)	Low normal	43	83 (12.75 Gm.)	7,650
9/2	Less than 5% 80 sec. +†	—	—	—	—	—	—	—
9/3	60% – 9 A.M. 80% – 3 P.M.	—	8 minutes, 45 seconds	1 minute, 15 seconds	Low normal	43 9 A.M.	88 (13.5 Gm.) 9 A.M.	3,200 9 A.M.
9/4	100% good large firm clot	—	—	—	—	—	—	—
9/5	100%	—	—	—	—	39	—	—
9/6	90%	No petechiae 6 minutes	—	—	—	—	—	—
9/7	100% good large clot	—	5 minutes, 35 seconds	—	—	38.5	—	—
9/8	100% good clot	—	—	—	—	—	—	—

*This test was probably in error.
†This test was probably in error. A later test showed a tiny fragile clot in 28 seconds. A subsequent test showed a normal prothrombin control of 13 seconds, a normal plus a prothrombin-free plasma of 37 seconds, and a normal plus patient's plasma of 18 seconds.

On June 2, 1952, the patient was admitted to Hartford Hospital with some bleeding and uterine cramps and was thought to be in labor. Pains and bleeding subsided and she was discharged the following day. From May 26, 1952, to June 24, 1952, she lost 3½ pounds and the abdomen became smaller. She continued to have pains, backache, and brownish vaginal discharge.

On July 12, 1952, sixty days after she had ceased to feel life she began having some bleeding and severe abdominal pains, which lasted about two hours. She was admitted to the hospital and delivered an extremely macerated (approximately 22 to 23 weeks), shrunken, brownish, disintegrating male fetus, with placenta and membranes complete, four minutes after admission. Ergotrate, gr. 1/320, was given intravenously immediately post partum and she was returned to her room. She immediately began to hemorrhage profusely. There were very few clots and these were small and of poor quality. Two 5 c.c. tubes of venous blood were taken and placed in an incubator at 37° C. These were examined at 20, 30, 45, and 60 minutes. There was a very poor and small clot, which did not adhere to the tube, and which sank to the bottom. The clot was not completely liquefied but seemed definitely to be at least half dissolved; and the pathologist was convinced that it showed definite evidence of diminished fibrinogen.

Saline, 500 c.c., and group 0, Rh-negative blood, 500 c.c., were given intravenously. Ergotrate, gr. 1/320, was given intramuscularly. The uterine fundus was well contracted and firm throughout, yet the patient continued to bleed profusely.

Blood for fibrinogen determination was drawn and 2 Gm. of fibrinogen in 500 c.c. of normal saline was given intravenously through a filter, requiring 10 minutes. A prothrombin time determination was done. The control showed a large firm clot in 13 seconds. The patient's blood showed a very small weak clot in 19 seconds. Prothrombin was 70 per cent. Blood taken from the patient at this time showed a trypsinized titer positive in 1:128 dilution.

Blood taken for determination of fibrinogen after the administration of fibrinogen was not drawn until the termination of a second transfusion of 500 c.c. of group A, Rh-negative blood.

The cessation of bleeding after the administration of the fibrinogen and the second transfusion was prompt and dramatic. The bleeding just prior to its cessation showed a much more abundant and firmer clot. Estimation of the blood loss was difficult, but it was believed to have been about 1,500 c.c. The blood pressure taken twice during the hemorrhage was 106/60 and 96/60. The patient did not go into shock, treatment having been instituted early in anticipation of hemorrhage, because of the assumed probability of afibrinogenemia or hypofibrinogenemia.

Observation of the patient eight hours post partum showed her to be stabilized, and there was no further hemorrhage.

This appeared to be a definite case of hypofibrinogenemia with prompt and dramatic control of hemorrhage by the administration of fibrinogen.

The patient's hematocrit on the third postpartum day was 33.4. Her recovery was rapid and uneventful. There was no further hemorrhage and she was discharged on the fourth day.

Examination after six weeks showed the patient to be fully recovered.

Comment

The first case reported by Weiner, that reported by Ratnoff, and the second of the three cases reported herewith all required hysterectomy to bring about ultimate control of the hemorrhagic phenomena. In the hysterectomized case of the present series fibrinogen was not readily available, and the operation was an emergency procedure. Fortunately, in spite of this lack of preparation with fibrinogen, hysterectomy and multiple transfusions brought about her recovery. However, now that fibrinogen is available, emphasis should be added to that given by Weiner, to the necessity of preparing patients preoperatively with fibrinogen.

Furthermore, it would seem that, as knowledge is gained concerning fibrinogen blood levels and with further experience in the use of this agent, cases may be brought under control and stabilized without the necessity of hysterectomy. However, should hysterectomy become necessary in women who already have normal children, it should put an end to further difficulties due to Rh isosensitization.

Ratnoff has raised the question of the advisability of performing hysterotomy prophylactically in these cases, in order to remove the dead fetus before hemorrhagic phenomena and evidences of coagulation defects appear. It would seem that, since only three of the first fifteen cases reviewed by Weiner showed these defects, this might not be considered a high enough incidence to justify this procedure. However, as more experience is gained, and since the risk of severe hemorrhage is so great, this may yet prove to be the safest method, since induction of labor in these cases is usually difficult or unsuccessful.

Several theories as to the mechanisms involved in bringing about this condition have been put forth. Toxic placental or fetal substances may depress the production of fibrinogen by the liver. Liver function tests in one of the cases reported by Weiner were normal except for a moderate elevation of urobilinogen.

Tagnon,[7] and Christensen[8] have suggested fibrinolytic digestion of plasma fibrinogen as a cause.

Weiner has suggested the possibility that thromboplastic material from the diseased placenta may get into the maternal blood stream and cause defibrination of the plasma. It is known that amniotic fluid is highly thromboplastic[3] and that it occasionally enters the blood stream, producing embolism and hemorrhagic phenomena.

Conclusions

1. Three cases of hypofibrinogenemia occurring in Rh-isosensitized multigravidas carrying dead fetuses have been added to those reported in the literature.

2. It seems apparent that this condition can be readily anticipated; and that for practical purposes a simple laboratory clot lysis test is sufficient to establish a diagnosis.

3. As further experience is gained the administration of fibrinogen may obviate the necessity for hysterectomy in these cases.

4. Re-emphasis is given to the need for adequate preoperative preparation with fibrinogen where hysterectomy is necessary.

5. The question of prophylaxis, such as hysterotomy, will probably not be answered until more is known concerning the incidence of this condition.

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A NOTE ON DEMAND FEEDING

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IT IS generally agreed that demand feeding per se is not a subject of great importance from a medical point of view. However, like many trivial subjects, its consequences have become important. Public enthusiasm and pressure from various groups interested in child psychology have to some extent forced the medical profession to adopt this method of infant feeding. It may be helpful to review briefly the consequences of this trend.

The basis for the widespread recent acceptance of demand feeding originated with the studies of Aldrich[1] and his associates at the Mayo Clinic. They investigated the causes and duration of crying in the newly born and listed the following sources: hunger, chilling, bright lights, peristaltic movements, vomiting, defecation, urination, loud noises, and loss of equilibrium. Included are two so-called negative causes: the need for fondling and the lack of rhythmic motion. They concluded that the cry of the newly born is a reflex protective mechanism used as a signal of need to whoever may attend him. They further stated that if the cry is ignored, it may lead to harmful omissions in the baby's care and accordingly recommended more nurses and a closer contact with the mother during the neonatal period. If by implication all cries should be heeded, then the answer to the hunger cry is demand feeding.

Since the appearance of Aldrich's publications in 1945, the enthusiasm for demand feeding has been almost incredible. It coincides with an ever-growing interest in psychiatry and an unfounded optimism in the belief that if one can get hold of the precipitating causes of emotional conflicts, the life of an individual can be shaped. Brenneman's[2] warning entitled "The Menace of Psychiatry" and Williams'[3] review of the limitations of psychiatry deserve re-emphasis. A few attempts were made to stem the tide, the most important being Bakwin's[4] article, "Self Regulation and the Mother," and the terse remarks by Irving,[5] who stated: "Recently a group of persons have appeared who are known as child psychologists. They maintain that a new-born infant should not be nursed at regular intervals but whenever it cries; otherwise, they say, it will suffer in later life a sense of frustration. How they know this they do not say. The characteristics of many American children, however, lead one to wish that there had been more instead of less family discipline, and that it had begun at the earliest possible age."

Bakwin[4] specifically described groups of mothers whose anxiety is increased by the demand-feeding regime. "Unaided by the sanction of a traditional approach, they are overwhelmed by a task which they are, for the time being, unable to handle." He describes the "orderly type" and the "executive type"

who derive great satisfaction from receiving precise prescriptions. His observations have been confirmed by many pediatricians. In the same article a discussion of child rearing in certain central and eastern European cultures emphasizes that children reared by methods far different from ours grow up to be adults who are, according to general observation, fully as happy and stable as we. In some of these communities children were prepared for the future by a long process of "hardening." Crying was believed to be good for the baby and thus, in contrast to Aldrich's conclusions, there exists a divergent mode of dealing with the same body of facts concerning human behavior. "Strange as these customs may seem to us," Bakwin observes, "they have not been psychologically traumatic in the long run." This is in accordance with Kanner's[6] teaching that discipline need not be feared as long as the child knows that he is "wanted."

It has become apparent that the majority of babies do well physically on either scheduled or demand feeding. Old records show that many physicians and hospitals individualized infant feeding and maintained a schedule. Under proper direction babies were not forced to eat a prescribed amount of formula; the intake was not restricted and the formula was adjusted to meet the natural appetite. Infants were fed at 2, 3, or 4 hour intervals and the prematures, ill infants, and babies with feeding problems had a wide variation in their schedules. It is the attitude of the physician that has changed. The proponents of demand feeding believe that a child should be fed whenever he appears hungry and they have lost interest in the problem of devising a formula and a routine that will permit the child to be satisfied for the longest possible interval. The result has been a deterioration in the art of infant feeding. It is simpler to compare the two methods by listing adverse effects. These represent, in part, the abuse of either method, but it becomes important to recognize which method lends itself more readily to abuse. Scheduled feeding is thought to make infancy less happy, child rearing more difficult, and emotional disturbances in later life more frequent. These suppositions remain unproved. Some adverse effects of demand feeding are listed below:

1. Parents and nurses are often unable to differentiate the hunger cry from other causes of crying.

2. The child frequently assumes a position of undeserved importance when the entire household is upset by irregularities in the feeding schedule.

3. It often constitutes the first step of a pattern of extreme permissiveness in general behavior.

4. Parents accustomed to demand feeding find difficulty in an abrupt adjustment to the rigid discipline of feeding and medication often required during an illness.

5. It becomes an easy excuse or way out if a badly constructed formula fails to satisfy an infant for intervals of 3 or 4 hours.

6. It is associated with an increasing tendency to blame the failure of infants to thrive in hospitals on emotional deprivation and scheduled feeding rather than on faulty medical and nursing care. Clinical manifestations of

emotional deprivation have never been observed during the first two weeks[7] of life and this fairly well-defined picture is chiefly confined to poorly managed asylums and institutions for homeless infants.

7. It increases anxiety in certain types of mothers.

During the past two years an increasing number of physicians have adopted a middle-of-the-road course in respect to the plan of infant feeding. They[8] state that it occupies a position between two extremes and cannot be outlined by definite or dogmatic rules. A close scrutiny indicates that the time required to establish this middle course is often about two or three months. This is the age at which the diminution in crying is usually spontaneous. Moreover, approximately 80 per cent of normal infants thrive on any reasonable regime and the superiority of a particular method is not easily proved. The inability to provide definite rules is a source of confusion to mother and nurse and makes the teaching of infant feeding extraordinarily difficult.

Summary

Some adverse effects of demand feeding are described. It is emphasized that no evidence exists to justify the abandonment of scheduled feeding.

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THE EFFECT OF RELAXIN ON THE EXCRETION OF DIODRAST IN THE CASTRATE HYSTERECTOMIZED RABBIT

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RELAXIN was first isolated and described by Hisaw,[1] who showed that this substance was responsible for the relaxation of the pelvic ligaments in pregnancy. The substance has been prepared from whole ovaries of sows, the uterus, placenta, and blood serum of other mammals, and from the blood serum of pregnant women.[2, 3] Recent attempts to extract it from human placenta have not been successful.[4]

The characteristic effect of relaxin in the castrated guinea pig was noted only after the animal had been primed and prepared by injections of estrogen. The histological changes occurring in the symphysis of the pregnant guinea pig which are presumed to be the effect of relaxin consist of a progressive vascularization, proliferation of connective tissue cells, lengthening of the ligament, and bone resorption toward the end of pregnancy.[2] The degree of relaxation of the pubic symphysis produced in the sensitized castrate guinea pig led to the present basis for the assay of relaxin at the present time.

The clinical significance of these experimental findings is apparent when one considers the pelvic relaxation which occurs in the pregnant woman. The normal width of the pubic symphysis in women is generally 4 to 5 mm., while during pregnancy there may be an increase of 4 to 6 mm. In some instances a symphysial gap of as much as 3.5 cm. has been observed in the last trimester of pregnancy.[5]

The effect of relaxin on tissues other than those of ligamentous structures has not been reported. The possibility that in general relaxin may alter smooth muscle is indicated by the physiological behavior of the ureters during pregnancy. The observed dilatation of the ureters in human pregnancy cannot be accounted for solely as the result of the pressure of the pregnant uterus against the exposed portion of the ureters as they cross the brim of the bony pelvis. Superimposed upon this factor is a condition of atony of the ureteral musculature which favors a slowing of urine flow from the secreting unit, a weakening of the ureteral jet, and a delay in filling as demonstrated by intravenous pyelography.

The results of studies of the effect of pregnancy on the urinary tract of animals are difficult to correlate with the changes seen in the human ureter during this period. One source of confusion is the fact that in quadrupeds the pressure of the pregnant uterus is almost without effect in contributing to ureteral dilatation. In 1936, Rossi[6] showed by intravenous pyelography in

rabbits that there is filling further down the ureters in pregnant than in nonpregnant animals. Of greater importance was the finding that, in the pregnant rabbit, there is a definite delay in the appearance of the greatest concentration of dye in the ureter following its intravenous injection. These studies were repeated by Crabtree, Abramson, and Robins[7] with the addition of a mechanical device with which they attempted to reproduce the pressure effects of the enlarged uterus acting on the ureters. They confirmed the earlier findings of Rossi and demonstrated that the pressure produced an additive effect in causing delay in filling of the ureters in the pregnant rabbit.

The present study was undertaken to determine whether exogenous relaxin would produce changes in the urinary tract of rabbits which simulated those of pregnancy.

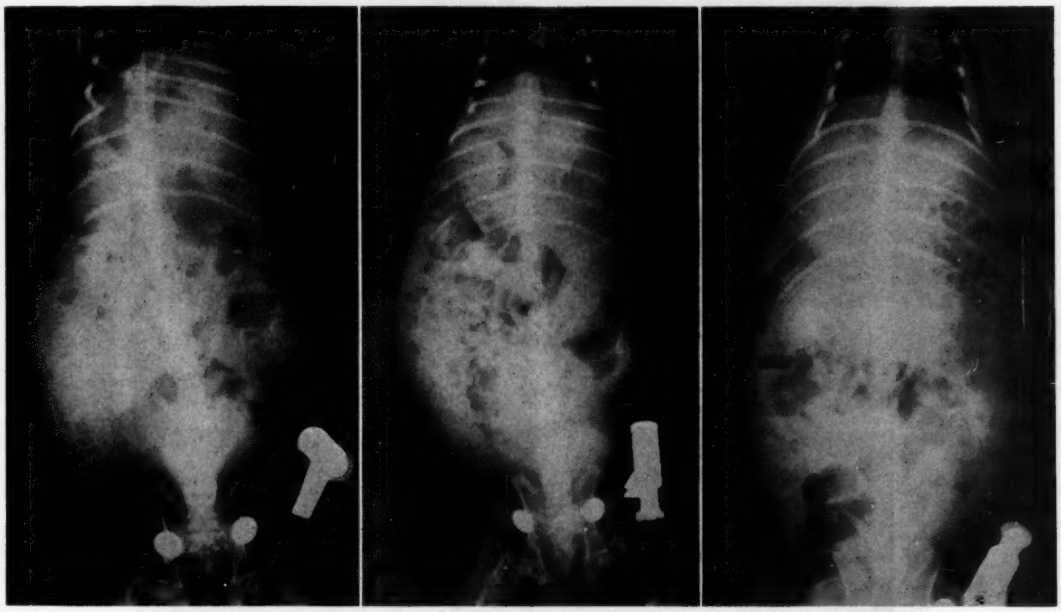

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Before castration, 3 minutes after Diodrast.
Fig. 2.—After castration, 5 minutes after Diodrast.
Fig. 3.—One week on estrogen, 6 minutes after Diodrast.

Intravenous pyelography was performed by the injection of 10 c.c. of Diodrast with an x-ray exposure of 50 kv. at $\frac{1}{30}$ second and a tube distance of 34 inches. An elastic device was used to produce pressure over the pelvic brim during exposure. The animals used were virgin does and after the initial pyelogram they were castrated and the uteri were removed. Pyelograms were then repeated (1) one week after operation, (2) one week after the daily administration of 1,000 I.U. of ethinyl estradiol, and (3) one and two weeks after the daily subcutaneous injection of both estradiol and 1,000 guinea pig units of relaxin.*

*Supplied through courtesy of Edward H. Frieden.

Figs. 1, 2, and 3 are pyelograms of the same rabbit taken before operation, 1 week after operation, and 1 week after daily subcutaneous injections of 1,000 units of ethinyl estradiol. There is no change in the caliber of the ureter. Furthermore, the bladder is already outlined at 3, 5, and 6 minutes, respectively, after injection of Diodrast. The ureter is outlined essentially in the upper half.

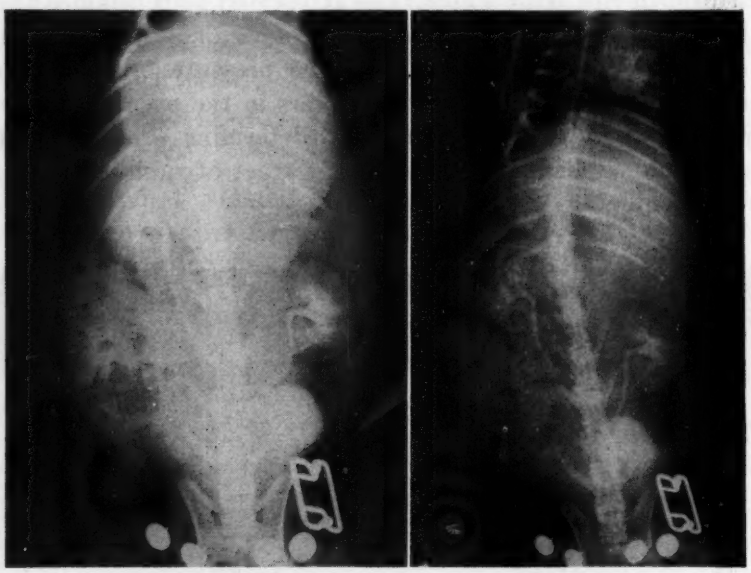

Fig. 4. Fig. 5.

Fig.4.—Three weeks on estrogen, 2 weeks on relaxin, 15 minutes after Diodrast.
Fig. 5.—Three weeks on estrogen, 2 weeks on relaxin, 20 minutes after Diodrast.

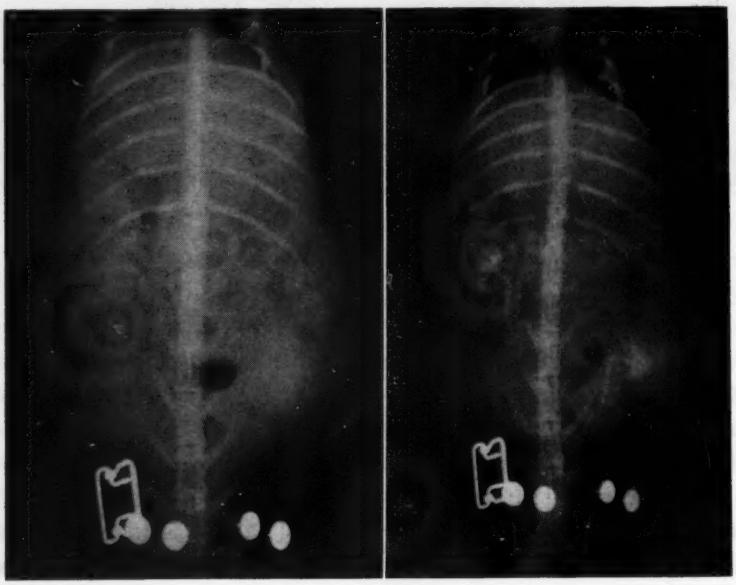

Fig. 6. Fig. 7.

Fig. 6.—Four weeks on estrogen, 3 weeks on relaxin, 6 minutes after Diodrast.
Fig. 7.—Four weeks on estrogen, 3 weeks on relaxin, 15 minutes after Diodrast.

In Fig. 4 is illustrated the x-ray after 3 weeks of daily administration of ethinyl estradiol and two weeks of relaxin. The best plate was obtained 15 minutes after injection of Diodrast. This shows the beginning of filling of the bladder and almost complete outline of the ureters and a definite increase in the caliber of the ureter.

Fig. 5 is the x-ray of this same rabbit taken 20 minutes after injection of Diodrast (5 minutes after Fig. 4). This demonstrates slightly increased bladder density over the 15 minute film.

Fig. 6 is the 6 minute x-ray of the same rabbit taken 4 weeks after ethinyl estradiol and relaxin administration. Here the bladder is not outlined and only the upper part of the right ureter is filled and about two-thirds of the left. Compare this with Fig. 7, taken 15 minutes after Diodrast, showing the beginning of bladder filling and almost complete filling of the ureter.

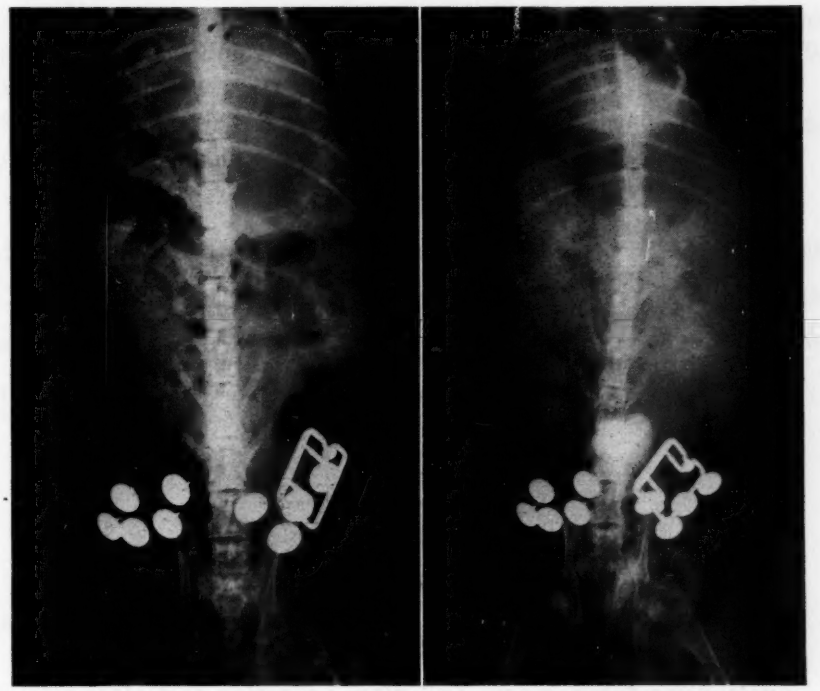

Fig. 8. Fig. 9.

Fig. 8.—Six minutes after injection of Diodrast and before operation.
Fig. 9.—Three weeks after estrogen-relaxin therapy, taken 25 minutes after injection of Diodrast.

Fig. 8 shows the pyelograms of a second animal taken 6 minutes after injection of Diodrast and before operation. Here the ureter on the left (low kidney) is filled down to the bladder and the bladder already has dye in evidence. This rabbit underwent the same routine as the other, namely, operation, administration of ethinyl estradiol daily for two weeks, and then injections of estradiol and relaxin daily for two weeks.

Fig. 9 shows the pyelogram of this rabbit three weeks after estrogen-relaxin therapy taken 25 minutes after injection of Diodrast. Here we note the first appearance of the dye in the bladder and the ureter is almost filled. Unfortunately, further plates were not taken, but, from what is seen here, undoubtedly the best plate showing full filling of the ureter with the dye

would have occurred at 30 minutes or more after injection of the dye. This illustration further demonstrates the variability in dilatation of the ureter.

As a control for the previous two rabbits, pyelograms were taken of a rabbit on the twenty-second day of gestation. Fig. 10 shows the pyelograms of this rabbit taken at 25 minutes after injection of Diodrast. The two ureters are filled almost completely but as yet the bladder shows no dye.

Animal experimentation on the ureter at best is most difficult. Many factors are present which cause variance in the results to some degree. Two undoubted factors here, as in human pregnancy, are marked variation of individual animals in response to pregnancy; and, as indicated by Hortolomei and associates,[8] the ureters have a tendency to fill more completely when the bladder is full.

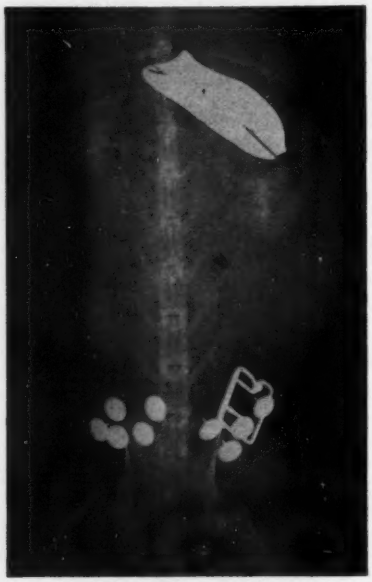

Fig. 10.—Pyelogram of pregnant rabbit taken 25 minutes after injection of Diodrast, on the twenty-second day of gestation.

The pyelograms taken before and after operation and after estradiol administration revealed the best concentration of dye in the films taken between 3 and 6 minutes after injection of Diodrast. In contrast are the findings following relaxin administration, in which cases the greatest concentration of dye appeared at 15 and 20 minutes.

As has been mentioned before, there is a double etiology in the changes noted in the ureter in pregnancy. The primary factor is atony of the musculature, and the second the pressure of the pregnant uterus against the exposed portion of the ureter where it crosses the brim of the bony pelvis.

In quadrupeds this pressure factor is for the most part, if not completely, absent. Thus it has been difficult in the absence of physiologically produced pressure to compare the changes in the ureters of pregnant animals with those of human beings. However, the presence of the primary factor of atony of the ureteral musculature in animals is of the greatest importance.

The delay in appearance of the dye in the entire ureter and bladder in hysterectomized ovariectomized rabbits treated with estrogen and relaxin compares favorably with that noted in the pregnant rabbit. It seems quite evident, therefore, that relaxin affects ureteral muscle to the point of making it atonic.

Summary

1. Intravenous pyelograms were taken of rabbits prior to and after hysterectomy and castration, after ethinyl estradiol administration, and following estradiol and relaxin administration.

2. Intravenous pyelograms were taken of a pregnant rabbit on the twenty-second day of gestation.

3. The pyelograms taken after relaxin administration demonstrated delay in complete filling of the ureters and appearance of the dye in the bladder comparable to that seen in the pregnant rabbit.

4. This delay in ureteral and bladder filling is due, we believe, to atonicity of the ureteral musculature caused by estradiol relaxin therapy.

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AN ATTEMPT AT PRODUCTION OF HYDRONEPHROSIS OF PREGNANCY, ARTIFICIALLY INDUCED

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THERE has always been some controversy as to whether the hydronephrosis associated with pregnancy is caused by hormonal changes, pressure phenomena, or both. In an attempt to prove or disprove the hormonal factor, it was believed that if a nonpregnant woman in the childbearing period could be given sufficient hormones of the type produced in the body by pregnancy, perhaps the side effect of pregnancy affecting the urinary tract could be produced without the pressure factor of a large uterus.

The frequency of hydronephrosis in pregnancy varies from 92 per cent (Strumpf[1]) to 100 per cent (Kretschmer[2]). This dilatation may begin in the sixth week of pregnancy in the primipara or the tenth in the multipara, and reach a maximum in the twenty-fourth week in the primipara or the twenty-second week in the multipara. The ureters are normal by the twenty-fifth postpartum day, but sometimes are so by 6 to 24 hours after delivery. Whitelaw[3] found 20 out of 23 patients completely free of dilatation or markedly improved by 1 week post partum.

Cruveilheir[4] in 1843 reported finding ureteral dilatation in women who died during the later months of pregnancy and in the puerperium. The early explanations of this phenomenon then were that changes were mechanical in nature, the pregnant uterus rising out of the pelvis with pressure on the ureters at the brim, the dextrorotation of the uterus and the sigmoid causing more pressure toward the right and more protection on the left. In 1928, Hofbrauer[4] did histological examinations of the ureters of women who died in pregnancy and concluded that the obstructions were intrinsic in nature. He found hyperplasia and hypertrophy of muscle and fibrous tissue of the ureter and periureteral sheath. Baird[4,a] in 1932 confirmed the finding of periureteral sheath hyperplasia, especially of the lower ureters, but the amounts of hyperplasia did not correspond to the degree of hydroureter. Also, though the hyperplasia was bilateral, the hydroureter was more marked on the right than the left. During a cesarean section on a uterus rotated to the left, Baird found, nevertheless, the right ureter dilated more than the left.

Traut[5] found that ureteral atony was directly proportional to uterine muscle atony; they both appeared and disappeared simultaneously during gestation. Atony appeared about the third month, was progressive up to the seventh, with a marked increase in motility in the last 2 months, associated with a moderate decrease in dimensions. After delivery, atony was marked up to the third week. There was no atony about the sixth to seventh week post partum. Therefore, hormones rather than mechanics seem to be the influential factors. The gall bladder disturbances associated with the decreased peristalsis are also attributed to the chemical influences of the hormones of pregnancy.

Lee and Mengert[6] cystoscoped 12 pregnant women, catheterized the ureters, and did retrograde ureterograms. They found no evidence of pressure on the ureters from surrounding structures. After 24 hours of ureteral catheter drainage, there was no change in the amount of hydroureter by intravenous urograms. Hundley[7] repeated the experiments of Lee and Mengert and found that catheter drainage of the hydronephrosis during the last months of pregnancy did not reduce the hydronephrosis in 24 hours, but did in 48 to 72 hours.

Carson[8] observed autopsies of pregnant women and found ureteral dilatation before organs were removed. He found the uterus lying on the right with ureteral dilatation above the point of pressure; the sigmoid seemed to protect the left ureter, and the right ureter was flattened by the uterus. Furthermore, by distending ureters with catheters in place, he was able to insert 15 to 100 c.c. (average 52.6 c.c.) on the right, and 6 to 80 c.c. (average 34.6 c.c.) on the left with a normal of 13 c.c. maximum. Microscopically, there was edema of the tunica propria, edema and round-cell infiltration of the inner muscular layers in the primiparas, thickening, edema, and congestion in the multiparas. Therefore, a mechanical block was intimated.

Hundley and associates[7] examined 13 women, 11 of whom died at term. In 12 of these, the hydroureter of the upper two-thirds of the ureters was found from the brim of the pelvis up, more so on the right than the left. The lower (pelvic) portions of the ureters were firm and rigid. The abdominal portions were flaccid, ribbonlike, with definite loss of tone. In microscopic sections, there was muscular hypertrophy, edema, and increased vascularity similar to the physiological changes in the generative tract during pregnancy. The hypertrophy was mainly of the external longitudinal sheaths of the ureter in the lower third (sheath of Waldeyer). They also found hydroureters in large ovarian and uterine tumors that rose out of the pelvis. They explained these by pressure, the right being larger than the left because of dextrorotation of the uterus and the sigmoid cushion. Also, the right ureter crosses the iliac vessels at a right angle, whereas the left is almost parallel.

Payne[9] showed that production of hydronephrosis by hormones in rabbits and dogs was unsuccessful. He also showed, though, that pregnant rabbits and dogs had no ureterectasis as shown by intravenous pyelograms. Rossi[10] claimed that a concentrate of blood serum of pregnant rabbits had produced characteristic ureteral and pelvic dilatation in nonpregnant rabbits in 48 hours, lasting for some days. Crabtree[11] found that there was in pregnant rabbits a suggestion of hydroureters and ease of ureteral dilatations not found in nonpregnant rabbits.

Eight Rhesus monkeys had fetuses removed by means of abdominal hysterotomy leaving the placentas behind, thereby separating mechanical from hormonal influences. Intravenous pyelograms were taken. Dilatation of pregnancy was found in 6 out of 8 cases. Of the 6, one became normal in 7 days with no interruption. In 3, the dilatation was sustained or increased while the placenta was in situ. After expulsion of the placenta, the dilatation decreased to normal when uncomplicated by infection. In 2, there was a marked increase in dilatation. After removal of the placenta, the ureters were normal. Therefore, dilatation can develop after removal of the fetus while the placenta remains in a functional state. Traut[12] concluded therefore that the hydronephrosis was primarily due to the state of pregnancy and secondarily to the weight of the uterus and its contents.

Van Wagenen[13] took 11 monkeys, also removed the fetuses and not the placentas, and found that the hydronephrosis persisted until removal of the placentas. Van Wagenen[14] also examined 3 Rhesus monkeys whose fetuses

died but the placentas remained functioning. He found the ureteral dilatation continued. Therefore, he concluded that "pyeloureteral dilatation in pregnancy is associated with the functioning of the maternal surface of the placenta . . . without dependence on the continued presence or life of the fetus."

Van Wangenen,[15] in another experiment, used 10 monkeys with 37 pregnancies. In one, there was maximal hydronephrosis with the first pregnancy, then decreasingly severe stasis thereafter, on the right side greater than on the left; this monkey was pregnant 9 times. With Theelin and stilbestrol, there were no changes in pregnant and nonpregnant monkeys. In 2 monkeys, late in pregnancy, there was no decrease in the amount of hydronephrosis. With progesterone (Proluton) for 30 days, there was no earlier appearance of dilatation nor was there inhibition of the usual decrease in size in the second pregnancies. Therefore, he concluded that there was a successive decrease in dilatation in progressive pregnancies, and hormones caused no influences.

Philipp[16] transfused blood from pregnant women to nonpregnant and caused ureteral dilatations.

Case No.	Hosp. No.	Age	Control I.V.P. 5/25/'49 to 6/3/'49	DRUG THERAPY BEGUN ON 12/6/'49	7 weeks I.V.P. 1/24/'50 to 1/28/'50	14 weeks I.V.P. 3/16/'50 to 3/17/'50	21 weeks I.V.P. 5/4/'50 to 5/9/'50	23 weeks I.V.P. 5/19/'50	24 weeks I.V.P. 5/29/'50	30 weeks I.V.P. 7/15/'50
1	MS 7113	26	Normal		No change	No change	Pressure deformity of roof of bladder			
2	MM 6256	35	Normal		No change	No change	No change			
3	VA 7289	40	Normal		No change	No change	No change			
4	MM 6251	30	Normal		No change	No change	No change			
5	SS 6254	28	Normal		No change	Pressure of roof of bladder by uterus	Same	Same		
6	MB 3112	35	Normal		Pressure deformity of roof of bladder	Same	Same	Normal		
7	RM 7114	33	Normal		Slight hydroureter	Same	Same	Same	Suggestive hydroureter	Normal
8	MD 3551	35	Right hydronephrosis		Same	Same	Same	Same		

DRUGS STOPPED

Fig. 1.

Lubin[17] took 30 postpartum women 24 hours after delivery. He found dilatation in 96.6 per cent on the right and in 46 per cent on the left; on the right alone in 53 per cent, on the left alone in 1 per cent. On the seventh day 30 per cent were normal, 13 per cent showed some regressions, 20 per cent, a slight change, and 30 per cent, no change. In 6 weeks, of 13 patients, all were normal. Posterior pituitary extract in 6 women caused 4 to be normal and 2

almost normal by the seventh day. Progestin in 5 out of 6 caused no change, and more dilatation in 4. A.P.L. and stilbestrol caused no marked variations from the normal. Therefore, regression of dilatation was increased by posterior pituitary, slightly affected by A.P.L., not affected by stilbestrol, and made worse by Progestin.

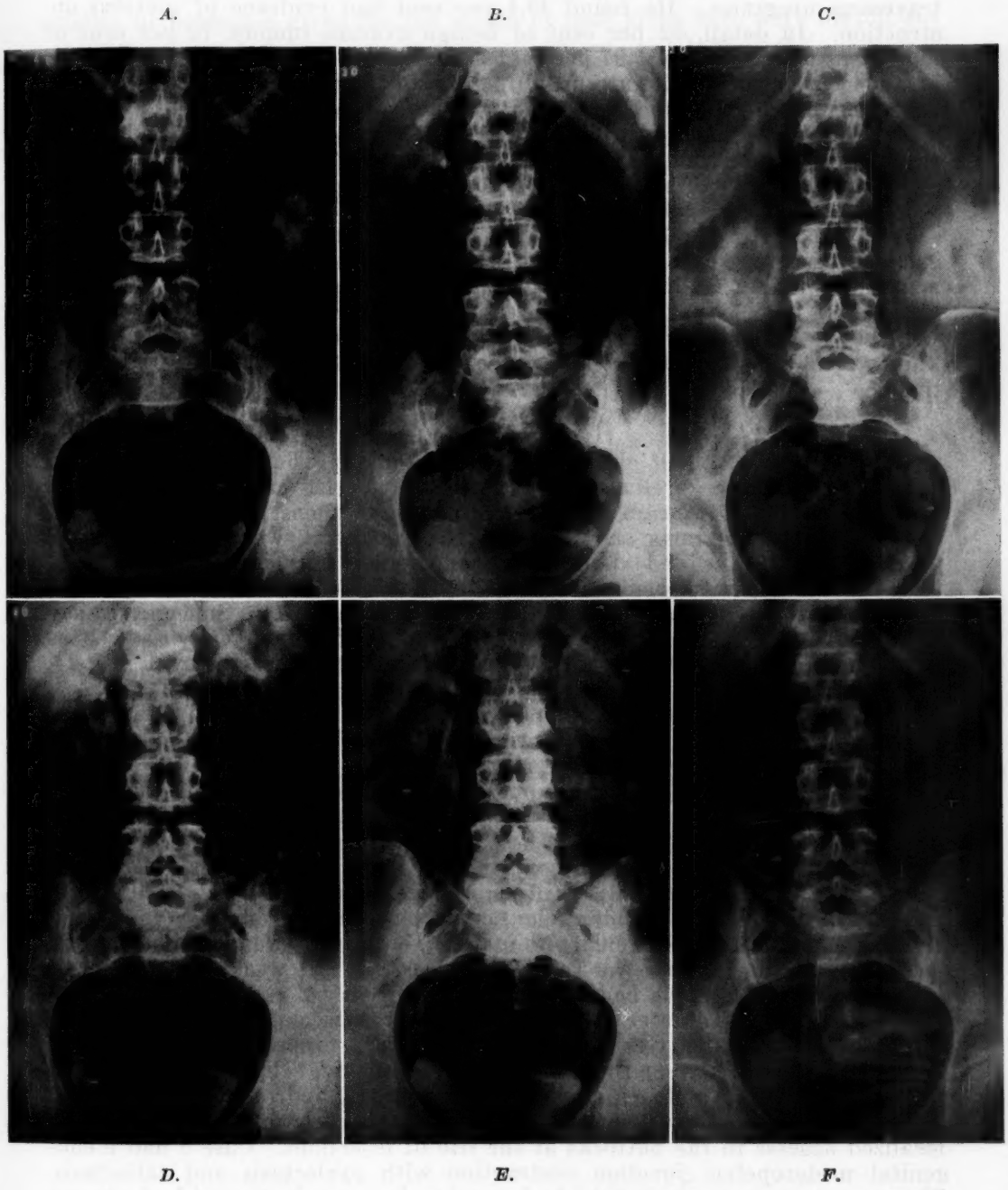

Fig. 2.—*A*, Pyelogram before treatment. *B*, Pyelogram at 7 weeks' gestation. *C*, Pyelogram at 21 weeks' gestation. *D*, Pyelogram at 23 weeks' gestation. *E*, Pyelogram at 27 weeks' gestation, 4 weeks after drugs had been stopped. *F*, Pyelogram at 30 weeks' gestation, 7 weeks after drugs had been stopped.

Karnaky (by personal communications) claims that "pyelograms on my patients receiving 100-800 mg. stilbestrol daily showed no dilatation of the ureters."

In nonpregnancy cases, ureteral obstructions due to pelvic diseases have been reported in varying percentages. Long[18] examined 379 patients by intravenous urograms. He found 49.4 per cent had evidence of ureteral obstruction. In detail, 52 per cent of benign ovarian tumors, 70 per cent of malignant ovarian tumors, 54 per cent of carcinoma of the cervix, 45 per cent of adenocarcinoma of the uterus, 50 per cent of pelvic inflammatory disease, 48 per cent of uterine fibroids, 40 per cent of cystoceles and uterine prolapses showed changes. Payne, in discussing Long's paper, noted that, in his own experience, 70 per cent of 96 patients with benign pelvic tumors showed pyelographic evidence of stasis. In his group, 72 per cent of those with myomas, 43 per cent of those with cysts, and 80 per cent with both cysts and myomas showed stasis. In those patients with intraligamentary tumors, 82 per cent had abnormal pyelograms. In both authors' series, all these changes were mainly right sided, and all were reversible after surgery.

Baker[19] and Kretschmer[20] also reported series of cases of hydronephrosis with pelvic tumors. Te Linde[21] recently reported a case of pelvic horseshoe kidney with repeated pyelograms during pregnancy without ureteral dilatations.

Material

Eight women, all of childbearing ages, four of whom were parous and three virginal, after preliminary pelvic examinations, endometrial biopsies, cervical and vaginal smears, catheterized urine specimens, blood counts, blood chemistry determinations and intravenous pyelograms, were given estradiol pellets, progesterone and chorionic gonadotrophic hormones in an attempt to reproduce natural hormonal secretion by the body during pregnancy. The exact dosage of each has been well described elsewhere.[22] Suffice it to say here that adequate signs of pregnancy were produced clinically as well as in the laboratory. Intravenous pyelograms* were taken at intervals: 7, 14, 21, 23 weeks.

Experimental drugs were stopped at the fifteen to twenty-third week due to lack of funds and/or drugs, as well as the onset of untoward side effects as described in another paper.[22] Our data are given in Fig. 1.

Since we had only a limited supply of hormones, it was deemed advisable to concentrate on only those cases showing evidence of suggestive changes by pyelograms. The first 4 cases showed no changes by the end of the fourteenth week, so therapy was discontinued in favor of the latter 4 cases; repeat pyelograms 7 weeks later still showed no changes in 3, and only a depression of the bladder in one. The next 2 cases showed bladder depression at 14 weeks (as if by an enlarged uterus) so therapy was continued to 21 weeks; no hydronephrosis was seen at 23 weeks. At 21 weeks, our supply of hormones ran so low, we had to concentrate on only 2 cases. Case 7 began showing slight hydroureter (right) at the seventh week, but it did not progress even to the twenty-third week. Drugs were stopped at this point. At 27 weeks (4 weeks later) there was only "suggestive" hydroureter. At 30 weeks (7 weeks after drugs stopped) there was no hydroureter seen. Clinically, this woman showed no changes from any of the others except for a localized abscess in the buttocks at the site of injections. Case 8 had a congenital ureteropelvic junction obstruction with pyelectasis and caliectasis. There was no progression of the hydronephrosis or production of hydroureter at the twenty-third week.

*The Neo-Iopax for the experiment was furnished by Schering Corporation, Bloomfield, New Jersey.

Fig. 2 shows the normal pyelograms and subsequent changes in the pyelograms during the period of treatment in Case 7.

Conclusions

The only conclusion that can be drawn here is that the amount and/or quality of hormones given for the length of time given here were insufficient to produce any definite ureteral changes. We do not believe the suggestive hydroureter produced in one out of eight cases to be significant. The bladder depressions produced in some of the others are indicative of an enlargement of the uterus.

There are several possibilities: (1) The specific hormone was not given; it may not be known yet. It may be a placental hormone not yet isolated. (2) The quantities of hormones were insufficient as to units per day and/or length of time given. It was impractical to give more because of the adverse toxic reactions and cost of the drug.

At some future date, this experiment will be repeated with the proper hormone and, we believe, will prove the theory of the hormonal influence. If and when it is so proved, a great step will be taken toward the relief and eventual cure of one of the complications of pregnancy. The hydronephrosis found in diseases other than pregnancy does not disprove this theory; it merely means that those conditions also produce hydronephrosis.

Addendum.—At this time, experiments have already begun with the use of relaxin. Results will be published at a future date.

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SPONTANEOUS RUPTURE OF A GRANULOSA-CELL TUMOR WITH MASSIVE INTRAPERITONEAL HEMORRHAGE

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SPONTANEOUS rupture of a granulosa-cell tumor with massive intraperitoneal hemorrhage is a relatively rare problem.[1-6] While ischemic necrosis with subsequent cystic degeneration and hemorrhage into the substance of the tumor itself is common, hemoperitoneum from rupture of the tumor wall is infrequent.[2, 6, 7] Torsion of the pedicle with hemorrhagic infarction of the tumor may produce serosanguineous or hemorrhagic ascitic fluid without a severe degree of intra-abdominal hemorrhage unless laceration of the capsule results.[8, 9, 10] In reviewing 700 cases of granulosa-cell tumors reported in the literature, Diddle[4] found that 2 per cent had some degree of intra-abdominal bleeding, but in only one-fifth of these was it extensive enough to require surgical intervention or result in death to the patient.

Laceration of the capsule with severe hemorrhage has been reported as occurring spontaneously,[1-3] subsequent to torsion of the pedicle[7] or trauma,[5, 6, 11] or following premature or full-term deliveries.[12, 13] Spontaneous rupture with massive hemorrhage is said to be peculiar to the granulosa-cell neoplasm because of the poor supporting framework for the granulosa elements and the minimal vascularity.[5, 14] Any rapidly expanding tumor, however, is subjected to accidental complications of its blood supply resulting in a weakening of its capsule from necrosis, cystic formations, necrotic hemorrhagic areas, or hematomas. Novak[15] states that the cystic characteristics of these tumors would be sufficient to explain the occasional occurrence of rupture without invoking any special susceptibility based on the properties of granulosal tumors, though the latter factor cannot be altogether eliminated from consideration.

Miss E. B., an 18-year-old single nulligravid Mexican woman, was admitted to the surgical service of Queen of Angels Hospital on Jan. 23, 1951, complaining of lower abdominal pain of two weeks' duration. Two months previously, she had noticed a mass in the left lower quadrant of the abdomen. This mass had increased markedly in size during the two weeks prior to admission. Her menses had been totally irregular for the past nine months, with several episodes of profuse bleeding which responded temporarily to injections given by her doctor. Prior to her present illness the menses occurred regularly every four weeks, lasted five days with moderate flow, and were painless. The date of her last menstrual period was Dec. 28, 1950.

Past history was essentially negative except for an appendectomy performed at 11 years of age.

Physical examination revealed a moderately obese, acutely ill woman with marked pallor. Pulse rate was 130; respirations 22; temperature 102° F.; and blood pressure 105/65. Heart and lungs were normal except for a soft systolic murmur over the precordium. The abdomen was distended and tender, especially over a mass palpable in the left lower quadrant. Rigidity was not marked. Pelvic examination revealed a tender mass, approximately 15 cm. in diameter in the left adnexal area, extending to the midline suprapubically. The cervix was posterior, mobile and slightly softened. The uterus was normal in size but pushed to the right. The

right adnexal area felt normal. Rectal examination confirmed these findings. An x-ray of the abdomen showed a large homogenous mass in the left lower quadrant producing an upward displacement of the intestines. No calcification was present in the mass. The hemoglobin was 7.8 Gm., red cell count 2.88 million, white cell count 15,800 with 82 per cent polymorphonuclear leukocytes. The urine was normal. A tentative diagnosis of an ovarian tumor with hemorrhage into the tumor was made and the patient was transferred to the gynecological service. She was given 1,000 c.c. of blood and started on penicillin. Twenty-four hours later the red cell count was 2.58 million with 6.8 Gm. of hemoglobin and the white cell count had risen to 25,000. The abdominal pain and tenderness had become more generalized.

At operation 1,500 c.c. of fresh and clotted blood was found in the abdominal cavity. The left ovary was found to be replaced by a hemorrhagic tumor mass approximately the size of a six months' gestation. At the left superior pole of the tumor mass, a 6 cm. rent in the capsule, from which fresh and clotted blood was exuding, was identified. No torsion was evident. The uterus and remainder of the adnexa were normal. A left salpingo-oophorectomy was performed, and the abdominal cavity was cleansed of blood and blood clots before closure.

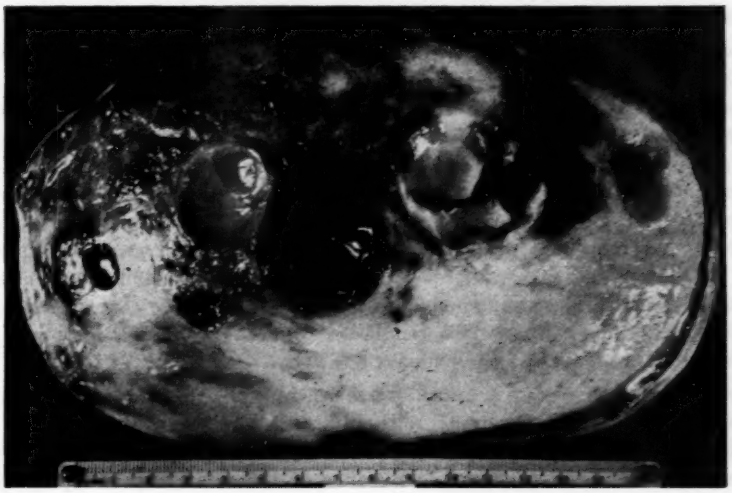

Fig. 1.—Photograph of the cut surface of the left ovary showing areas of pseudocystic degeneration, necrosis, and hemorrhage.

Pathological Report.—The specimen consisted of a large left ovarian predominantly solid but cystic mass, measuring 24 by 18 by 12 cm. The external surface was smooth for the most part. On one side there was a large, irregular rent through which abundant blood clot protruded. The cut surface showed a large circumscribed tumor measuring 23 by 13 cm. At one end a narrow, crescent-shaped portion of displaced ovarian parenchyma was identified. The cut surface was variegated, partly dark red, partly yellowish gray. In the central portion there were several cystic formations varying in size up to 4 cm. in diameter. They contained bloody coagulum. Just beneath the large rent previously referred to, there was an irregular area of pseudocystic degeneration measuring 9 cm. in diameter. The lining surface was irregular and trabeculated.

Microscopic examination of four representative sections of the ovarian mass showed in two of the sections abundant, well-preserved tumor tissue composed of numerous closely grouped cells, more or less uniform in size and shape. Some of the cells occurred in solid masses. Others were seen in slender anastomosing cords, presenting a cylindromatous pattern. In a few areas there was also a suggestion of a microfollicular pattern of arrangement of the cells. The nuclei were uniform in size, predominantly round, and while some were hyperchromic, there was no appreciable degree of pleomorphism. In places the supportive stroma was rather scant. In other areas the stroma was abundant and edematous in

appearance. There were a few scattered areas of degeneration, necrosis, and hemorrhagic infiltration. At the periphery of one of the sections was some edematous compressed adjacent ovarian parenchyma.

Diagnosis.—Large granulosa-cell tumor of the left ovary with areas of degeneration, necrosis, and hemorrhage.

The patient was given a total of 2,500 c.c. of blood. Her postoperative course was uneventful.

The follow-up period has been 18 months, with no signs of recurrence.

Comment.—The malignant potential of a granulosa-cell neoplasm is difficult to evaluate because of the delay in recurrences. Novak and Brawner[16] reported a clinical malignancy rate of 28.1 per cent, a figure which has been fairly well substantiated by other investigators.[18-20] More than a third of the recurrences, however, occur after five years, so that statistics based on a five-year survival are inaccurate. Jones and Te Linde[17] reported three patients who died from recurrences eighteen, twenty, and twenty-one years after removal of the primary tumor. Aimes and associates[18] reported the excision of a retroperitoneal mass of similar histological pattern thirty-three years after the primary removal of a granulosa-cell tumor from a girl 8 years of age.

Rupture of a granulosa-cell tumor results in the contamination of the peritoneal cavity with potentially malignant cells. Because of the rarity of this complication, only meager statistics are available as to the effect of such spillage upon the subsequent course of the disease. French[6] reviewed the literature and found fifteen such cases available for study. Ten patients were alive without recurrences from two to ten years; one patient was living and well at seventeen years following two operations for recurrences at nine and eleven years; three patients died in four years or less (one of metastases to the brain and two from abdominal recurrence) and one patient died in eight years of apparent pelvic recurrence. French[6] added a case of his own in which a return of normal menses and fertility followed a unilateral salpingo-oophorectomy, with the patient remaining well four years postoperatively. The tumor cell remnants apparently may or may not retain their viabilty following the removal of the primary growth.

The treatment of choice of a granulosa-cell neoplasm, ruptured or unruptured, in the older age groups, is total hysterectomy with bilateral salpingo-oophorectomy. Total ablation of the female organs is undesirable in the younger age groups, so that unilateral salpingo-oophorectomy has been advocated. Because of the relatively benign nature of many of these tumors and the slow rate of growth of recurrences, the preservation of the childbearing function appears justifiable in the young patient, especially when the neoplasm is well encapsulated. Whether simple excision is justifiable when the tumor has ruptured will depend upon the follow-up reports of cases so treated. However, as more and more complete data accumulate, the more clinically malignant these tumors appear, so that any woman treated for such a tumor of the ovary, whether by a complete or incomplete operation, deserves a careful periodic evaluation for the rest of her life.

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7100 SOUTH VERMONT AVENUE.

SICKLE-CELL ANEMIA AND PREGNANCY

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(From the Obstetrical Service of the Beth Israel Hospital, Boston, Mass.)

AMONG the familial hemolytic disorders found only in the Negro race, sickle-cell anemia ranks first in its diversity of presenting signs and symptoms. In recent reviews,[1, 2] approximately 70 cases of sickle-cell anemia and pregnancy have been reported.

The association of pregnancy and sickle-cell anemia is very serious. Fouché and Switzer,[3] on reviewing the literature, found 9 maternal deaths in 29 cases. Beecham and Beecham[2] added 37 more cases and noted 4 maternal deaths. Thus, in 66 cases there were 13 deaths (20 per cent). In other words, one out of five women with sickle-cell anemia will die if she becomes pregnant. The causes of death were infections in 7 cases (pneumonitis, nephritis), congestive heart failure in 4 cases, and crisis with thrombosis in 2 cases. In addition these patients are seven times more likely to go into premature labor, six times more likely to have a stillborn child, two times more likely to have a morbid course, and two times more likely to have toxemia than the average obstetrical patient.[2, 3]

Because of the paucity of cases, the relatively infrequent association with pregnancy, and the poor prognosis for the mother and infant, the following case is presented.

T. P.—(BIH M29295) This 22-year-old gravida i, para 0, Negro woman has had frequent episodes of sudden onset of arthralgia, myalgia, crampy abdominal pain, tachycardia, and fever since the age of 2 years. Her parents were told that she had a murmur and a diagnosis of rheumatic fever was made. She remained in bed for 3 to 4 months. She had repeated bouts of this nature. In 1948, during one of these episodes she was hospitalized at the Boston City Hospital and was found to have sickling of the red cells. A diagnosis of sickle-cell anemia was made. In 1950 while she was training as an x-ray technician at this hospital, the diagnosis of sickle-cell anemia was confirmed. There was no family history of similar symptoms or known sickling.

The patient was first seen in the prenatal clinic in January, 1952. Her last menstrual period was July 22, 1951; the estimated date of confinement was April 29, 1952. She stated that during the first trimester she had had some blurring of vision, nausea, vomiting, and headache. There had been no edema. These symptoms had subsided and at the time of admission to the clinic she was symptom free. The blood pressure was 136/74. The hemoglobin was 11.7 Gm. and the red cells were positive for sickling. She was Rh negative with no titer. Her husband was Rh positive.

Her course in the clinic was essentially uneventful except that the hemoglobin dropped to 9.5 Gm., with a 3.8 million red count, in February, 1952. She was followed by the hematologists who felt that she had a combination of sickle-cell anemia plus the "physiologic" anemia of pregnancy. Two weeks prior to admission to the hospital, at 36 weeks of pregnancy, she noticed the onset of dyspnea, two pillow orthopnea, and night sweats. On April 4, 1952, one day prior to admission, she noted the onset of acute abdominal pains and pains in the arms and legs. She felt quite weak and described this episode as being exactly like her usual sickle-cell attacks. There were no chills, nausea, vomiting, and the urine was not dark. On April 5, 1952, she was admitted to the medical service with a diagnosis of sickle-cell crisis.

Physical examination revealed a well-developed, well-nourished pregnant woman in severe pain, and appearing acutely ill. The respirations were rapid. There were no cough, no scleral icterus, no skin ulcerations, and no adenopathy. The blood pressure was 130/75.

The heart was not enlarged and there were no murmurs. The lungs were clear. The uterine fundus was up to the height of a 37 weeks' pregnancy; a breech was presenting and the fetal heart was in the right upper quadrant. There was generalized muscle tenderness. The reflexes were equal and active. There was no edema.

The urine examination was negative. The hemoglobin was 9.1 Gm.; white blood count 12,400; nonprotein nitrogen, 22 mg. per cent; serum bilirubin, 0.8 mg. per cent; thymol turbidity test, 2.6; clotting time, 17 seconds; bleeding time, 3 minutes; prothrombin time, 96 per cent of normal; and the tourniquet test was negative.

She was placed on oxygen by mask and given Demerol for the pain. She continued to have multiple joint pains. On April 7, 1952, she developed marked dyspnea. Examination of the lungs revealed dullness, decreased breath sounds, and moist râles at both bases. X-ray was negative. X-ray of the skull was normal with no evidence of sickle-cell changes. The left knee joint became swollen and her symptom complex continued. Not until her fourth hospital day did any evidence of hemolysis, consistent with sickle-cell crisis, appear (Table I). On April 12, 1952, she received 500 c.c. of whole blood without reaction but no improvement in the hemoglobin occurred. She developed severe precordial pain and pain in the back and chest. The baby was very active and spontaneously rotated to a vertex position. The chest symptoms continued and on April 15, 1952, x-ray of the lungs revealed a small, ill-defined area of consolidation in the left lower lung field. Electrocardiogram was normal. It was felt that she had a pulmonary infarction due to thrombosis. Her blood pressure during this time averaged $\frac{130\text{-}140}{90\text{-}100}$.

TABLE I. LABORATORY RESULTS IN CASE OF MRS. T. P.—SICKLE-CELL ANEMIA AND PREGNANCY

DATE	HEMOGLOBIN GM./100 C.C.	RED BLOOD COUNT	WHITE BLOOD COUNT	PLATELETS	RETICULOCYTES	SERUM BILIRUBIN	URINE URINOBILINOGEN	MISC.
4/ 5/52	9.1		12,400			0.8		Thymol 2.6
4/ 6/52	9.7	2.9	9,550	Normal				
4/ 7/52					1.9%	0.9	+1/10	
4/ 8/52			5,950					
4/ 9/52	9.7			Normal	2.7%	1.8	+1/160	
4/10/52	8.4							BSP 16%
4/11/52	8.6							
4/12/52	Transfused with 500 c.c. of blood							
4/14/52	8.8				0.9%	1.1	+1/320	
4/17/52	Delivery							
4/18/52	9.7	3.0		Normal	4.7%	2.5		
4/21/52	9.4	2.5		Normal	1.8%	0.9		
4/24/52	10.8	3.1	7,000	Normal	5.5%	0.8		

On April 17, 1952, the membranes ruptured spontaneously and the patient went into labor. She was started on procaine penicillin 600,000 units twice a day. During labor she had marked dyspnea. There were marked dullness and bronchial breath sounds in the left posterior chest. She was given oxygen by mask throughout labor. After ten and one-half hours, normal spontaneous delivery of a living child was accomplished under pudendal block anesthesia. The placenta grossly appeared normal. Microscopically, it showed massive sickling of red cells in the maternal sinuses but the blood in the fetal vessels appeared normal. On April 18, 1952, the patient showed the greatest evidence of hemolysis as demonstrated by laboratory tests (Table I). X-ray showed increased consolidation in the posterior portion of the left lower lobe. For 3 days post partum she had dyspnea but no joint pains. On April 21, 1952, the chest symptoms subsided, and clinically the dullness appeared less. The serum bilirubin markedly decreased and the hemoglobin rose. Examination of the baby's blood showed no evidence of sickling on April 20, and April 24, 1952. On April 25, 1952, x-ray of the chest showed resolution of the area of consolidation. The patient was discharged on the twelfth

postpartum day, symptom free. She was seen in the follow-up clinic in May and July. The blood pressure was 140/90. The smear was doubtful for sickle cells. The baby's blood was negative for sickling.

Comment.—In the case reported, the patient had a borderline blood pressure (140/90), but never manifested any albuminuria or edema. As such patients are very prone to develop toxemia, she was closely watched for the first sign of its development.

During the hospital stay she received oxygen. Reinhard and associates[4] have shown that by increasing the percentage of inspired oxygen, the degree of intravascular sickling may be decreased. However, there was no dramatic relief in this case and the patient developed a pulmonary infarction, probably as a result of thrombosis.

The delivery was conducted with the aim of minimal trauma, avoidance of anoxia, minimal blood loss, and prevention of infection. Local anesthesia was used and is probably the anesthesia of choice in these cases.

As yet the prognosis of children born to mothers with active sickle-cell anemia cannot accurately be stated. Beecham[2] reports that of 31 offspring studied, 10 were positive for sickling. It must be pointed out that some of the determinations were done on newborn infants in whom there is usually a paucity of sickle cells. The offspring in the case reported has not shown any sickling up to the present time (July, 1952).

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1093 Beacon Street

LITHOPEDION

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THIS is a report of a case of lithopedion of three years' duration at the time of operation.

The patient was a 27-year-old Negro woman, seen by me for the first time on June 20, 1949, complaining only of low back pain of two months' duration. A large abdominal mass was felt and, when questioned about this, she stated that it had been present since 1946 and that she had been told that she had a "stonebaby" in the abdomen. This had never caused discomfort and her menses had been normal.

An accurate history was not obtained until it was realized that she had used several different names during her previous hospital admissions, and had visited numerous doctors during the pregnancy to be described.

The last menstrual period occurred on Jan. 17, 1946. She was hospitalized on April 29, 1946, because of vaginal bleeding, fever of 100° F., and abdominal pains. She had fainted several times in the last three months, and the vagina was packed by a local doctor one month previously because of a threatened abortion. The hospital record showed that the abdomen was greatly distended and exquisitely tender. The cervix was large, soft and tender. The fundus could not be palpated. The hemoglobin was 5.0 Gm., red blood cells 1,470,000, white blood cells 9,000, and sedimentation rate 14 mm. in one hour. The impression was: incomplete abortion. She was given a sulfonamide compound and penicillin, and was discharged on May 2, greatly improved.

Fig. 1.

Apparently there were no more complications until she was admitted on Aug. 12, 1946, under a different name. At this time she was complaining of vaginal bleeding and minimal pelvic pain. An x-ray revealed a fetus of 32 weeks' size, presenting by the breech. The patient admitted that she had tried to abort three times during the pregnancy and planned to abandon the child when born. On this admission the hemoglobin was 12.5 Gm., white blood cells 12,500. The bleeding and pains subsided and she was discharged.

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On Dec. 10, 1946, she was readmitted under a different name. She stated that she had bled moderately for two weeks in November, and that it had now recurred. She had last felt fetal movement on October 21. Since then her breasts had decreased in size and she had noticed milk formation. An x-ray film revealed "intrauterine death of the fetus." There was marked deformity with overriding of the cranial bones. It was suggested that the fetus had died at the seventh or eighth month of gestation.

The patient was given a course of stilbestrol, which made her nauseated and two courses of intramuscular Pituitrin. The cervix was firm and closed. She was told that the fetus was dead and that she must wait for labor to ensue. When labor did not start in, she was discharged on Dec. 21, 1946, and was not seen again until the present admission.

Fig. 2.

Laboratory data at the time of the present admission were normal. An abdominal x-ray film revealed a lithopedion. Salpingograms (Fig. 1) revealed an elongated right Fallopian tube, with the Lipiodol extending well into the right iliac fossa. This suggested right tubal distortion associated with an old right tubal pregnancy which had resulted in a lithopedion. It was decided that an exploratory laparotomy was indicated.

At operation on June 23, 1949, the uterus was found to be normal in size. The right Fallopian tube was greatly elongated and intimately adherent at its fimbriated end with the head of a partially calcified fetus, the remainder of which lay transversely in the abdominal cavity, adherent only to the omentum and to the posterior pelvic peritoneum by a few fine filmy adhesions. A right salpingectomy was performed and the fetus was removed (Fig. 2).

The fetal weight was 1,100 grams. The crown-rump measurement was 24 cm., the crown-heel 44 cm. The head and necrotic placenta were encased in the fimbriated end of the right tube, which was 12 cm. in diameter. The mid- and proximal portions of the tube were normal.

The postoperative examinations were normal. She soon became pregnant again and was delivered of a full-term normal fetus on Feb. 26, 1951.

CIRCUMCISION CLAMP

DEAN SHELDON, M.D., SANDUSKY, OHIO

(From the Good Samaritan Hospital)

THE circumcision clamp displayed in the accompanying photograph has been used successfully at Good Samaritan Hospital, Sandusky, Ohio, on 200 circumcisions. The entire process of circumcision required one to one and a half minutes, we have had no instances of bleeding, and the final results are excellent. The principle involved is crushing of the foreskin between clamp edges which are dull enough to avoid cutting but sharp enough to destroy the small blood vessels in skin and mucous membrane. The safety, ease of application, and general simplicity have made the procedure attractive to those of us who have employed the clamp. We feel that the end results are as nearly perfect as can be hoped for and effected.

Fig. 1.

For several years we have been endeavoring to develop some type of instrument which would simplify circumcision. We are all acquainted with the cumbrous procedure of the classical "clamp" and "suture" methods. We are equally conscious of the many pitfalls involved in circumcision with various mechanical devices hitherto marketed and used. Circumcision by either of the techniques before mentioned is awkward and time consuming, and the end results often unsatisfactory.

The clamp was produced by a local manufacturer.

ENDOCERVICAL SPIRAL CURETTE

HARRY J. GREENE, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Kings County Hospital)

THE instrument shown* has been in use by me to complement the Papanicolaou vaginal smear and the cervical biopsy.

The instrument is introduced into the cervical canal in the same manner as one would apply the olive tip during tubal insufflation. With several turns it establishes a grasp in the lumen of the canal and advances by slow turns as would a screw. The thread insinuates itself in the cervical and endocervical tissues. Secretion and cells are expressed on the flat of the threads and in the grooves between the threads. When the entire length of the spiral instrument is in the canal, the base is in contact with junctional epithelium of the external os. It is now withdrawn with an unscrewing motion.

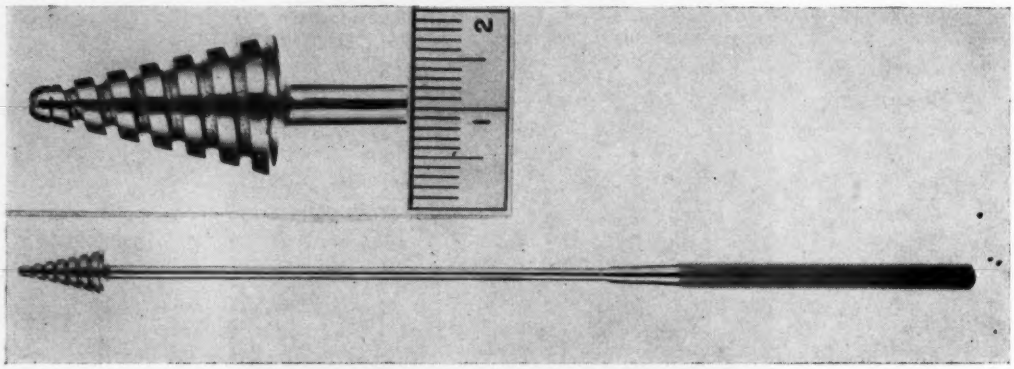

Fig. 1.

The spiral is rolled out on a glass slide, thereby depositing the contents. The slide with its contents is immediately immersed in the fixing solution and the Papanicolaou staining technique is followed. The remaining tissue in the grooves is removed with forceps and placed into tissue-fixing solutions and the routine slides are made for pathological evaluation.

The instrument is especially adaptable in the lacerated, everted, and hypertrophied cervix. The use of a tenaculum to anchor the cervix is rarely needed. Bleeding is minimal. Pain is not common. On occasion I have been able to avulse small endocervical polyps.

855 OCEAN AVENUE.

*Obtainable from the Sklar Manufacturing Company, Long Island City, New York.

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Selected Abstracts

Cancer, Malignancies

Limon, Jose Noriega: Cervical Cancer Complicating Pregnancy, Ginec. y obst. de México 7: 9, 1952.

The author reports on thirteen cases of pregnancy complicated with cervical cancer. He emphasizes the anatomopathologic and obstetrical clinical characteristics of the cases. The methods of treatment are well evaluated and varied:

Two cases at term: cesarean section followed by radiation.

One case at 9 weeks: radium (6,000 mg. hr.) followed by curettage and deep x-rays through four ports.

One case at 20 weeks: Wertheim followed by radiation.

Three cases at 27 to 32 weeks: intracervical radium, waited for viability, cesarean section followed by radium and deep x-ray.

Three cases at puerperium: one pelvic exentration, one radium and deep x-ray (1 year later pelvic exentration) and one radium and x-ray.

One case at 19 weeks: waited five months, then cesarean section followed by radical hysterectomy.

One case at 7 months with dead fetus: hysterectomy (radical) followed by deep x-ray.

One case at 28 to 30 weeks: waited three weeks, then cesarean section done followed by deep radiation.

At the end of one year twelve patients were alive and one dead. Of the four cases that received radiation while the fetus was in utero one fetus (9 weeks) died in utero and was removed by curettage. The other three (27 to 31 weeks) were extracted by cesarean section; one died 20 hours post partum of pulmonary atelectasis. Another apparently normal for three months died of gastroenteritis due to lack of maternal care. The other is still alive and normal in all respects.

RICARDO L. GORBEA

Zuckerman, C.: Pregnancy and Mammary Cancer, Rev. mex. de cir., ginec. y cancer 19: 363, 1951.

The author reports on a small series of four cases of pregnancy complicated by the presence of mammary cancer and the concepts derived therefrom. He believes that pregnancy is not a determining factor of mammary cancer but that its presence stimulates the growth and propagation of the mammary lesion. The author recommends that a patient who has or has had cancer of the breast should not become pregnant. He states, too, that in the presence of mammary cancer pregnancy should not be terminated but the mammary cancer should be treated as if the pregnancy were not present. He does not advise using any androgen therapy or radiation to the ovaries.

RICARDO L. GORBEA

Hertz, R., Cromer, J. K., Young, J. P., and Westfall, B. B.: Observations on the Effect of Progesterone on Carcinoma of the Cervix, J. Nat. Cancer Inst. **11**: 867, 1951.

In monkeys, progesterone prevents the development of the squamous metaplasia ordinarily produced by giving large doses of estrogen. Similarly, progesterone prevents the formation of estrogen-induced fibroids in guinea pigs, and may retard the formation of fibroids in women.

With this background, and with the precedent of hormone therapy for prostate and breast cancers, the authors have administered progesterone to 18 women suffering with carcinoma of the cervix. Two hundred fifty mg. in oil was given daily for periods ranging from 10 days to 5 months (average of 63 days or 15.75 grams).

In one patient the disease progressed unchecked, and in 6 the effect was dubious, but in 11 patients there were distinct visual (checked by serial photographs) and palpatory evidences of regression. These were: (a) reduced size, (b) reduced vascularity and friability of the lesion with epithelization of raw surfaces, and (c) markedly increased pliability of the previously rigid parametria. Histologic study does not reveal the morphologic basis for these changes.

The authors do not consider this evidence sufficient to warrant the use of progesterone as a therapeutic agent in carcinoma of the cervix. They feel that it does show that cervical cancer can be substantially altered by progesterone. This chemotherapeutic aid is offered to stimulate the search for synthetic steroids with "antitumorigenic" effects.

IRVING L. FRANK

Newell, James W., and McKay, Donald G.: A Clinical Review of Carcinoma of the Vulva, West. J. Surg. **60**: 388, 1952.

Recent advances in the understanding and recognition of premalignant states have altered the course of management in carcinoma of the vulva. Carcinoma of the vulva, however, continues to be one of the most lethal types of cancer. Diagnosis is usually possible on the basis of history and physical examination. The only predisposing factor upon which most authorities agree is that leukokraurosis is a frequent forerunner of carcinoma of the vulva. The prevention of carcinoma of the vulva at present consists of recognizing and adequately treating all leukokraurotic lesions which in turn will provide adequate control for about four-fifths of those destined to develop the disease.

When carcinoma once develops it becomes necessary to adopt a broad and radical surgical attack irrespective of the size of the primary lesion or the duration of symptoms. The histologic grade has little significance since lymph node metastases apparently remain independent of all these factors.

WILLIAM BICKERS

Sherman, Alfred I., and Ruch, Robert M.: The Effect of Lymph Node Metastases on Prognosis for Carcinoma of the Cervix and Vulva, South. M. J. **45**: 703, 1952.

Treatment failures in carcinoma of the cervix and vulva usually result from failure to eradicate lymphatic metastases. The control of lymph node spread, therefore, has become the major clinical problem in treatment. All cases of carcinoma of the cervix and vulva at the Barnard Free Skin and Cancer Hospital and the Barnes Hospital at St. Louis have been reviewed.

The cases were studied on the basis of histology of the regional lymph nodes which were removed at operation. A total of 176 cases of cervical carcinoma treated by pelvic lymphadenectomy in conjunction with irradiation of the primary lesion are reviewed. In addition there were 77 cases treated by radical hysterectomy with removal of the pelvic nodes. A total of 99 cases of carcinoma of the vulva are reported wherein vulvectomy alone was performed in 25. Vulvectomy and extensive deep pelvic node dissection were done in 74 patients.

The effect on prognosis of lymph node metastases in carcinoma of the cervix and vulva and the results of various methods of treatment are discussed. Among 253 patients with Stage I and II cancer there were found positive nodes in 21.7 per cent. Only 10.9 per cent of those patients survived 5 years as compared with the survival of 52 per cent for those in whom the lymph nodes were negative for carcinoma. Among 99 patients with vulval carcinoma 74 were treated by vulvectomy and lymph node dissection. Positive nodes were found in 43.2 per cent. Only 15.6 per cent of these patients survived 5 years as compared with 52.4 per cent of those who had negative nodes.

WILLIAM BICKERS

Zeitz, H.: Positive Lymph Gland Findings in the Wertheim Radical Hysterectomy, Geburtsh. u. Frauenh. **12**: 804, 1952.

For a long period of time the Wertheim radical hysterectomy for cervical carcinoma was abandoned in favor of radiation therapy. However, because of improvements in surgical technique, in anesthesia, and in blood transfusions, and because of the lowering of infection by means of the newer antibiotics, this operation, together with radical lymph node dissection, has again been popularized as the treatment of choice in carcinoma of the cervix. Similar improvements in the dosage and usage of x-rays and radium have also resulted in improved results in therapy. The question, however, as to which method is the best, or whether combined therapy offers added advantages, has never been fully exploited. This is especially true where the lymph glands are involved. In general it was felt that in International Classification Group I, 20 to 25 per cent positive glands must be expected; in Group II, 30 to 35 per cent involvement; in Group III, 40 to 50 per cent; and in Group IV, over 60 per cent.

Studies were made at the Heidelberg clinic on a group of 133 cases which were classified as Stage I and Stage II carcinoma of the cervix which were treated by radiation therapy alone or radiation plus radical definitive surgery of the Wertheim type. Cases were treated alternately except in those instances where the general physical status (diabetes, hypertensive heart disease, kidney disease, etc.) did not warrant more than radiation therapy. A comparison of three-year, five-year, or longer cures showed that no differences in results were obtained. Equal numbers of patients were living, without recurrences or metastases, when radiation was used alone, or when radical surgery was followed by radiation therapy.

L. B. WINKELSTEIN

Zuckermann, C., Urutia, M., and Graham, J. C.: Present-Day Knowledge of Cancer in Situ of the Uterine Cervix, Rev. mex. de cir., ginec. y cáncer **20**: 3, 1952.

The authors review the literature as well as the historical background on the subject and come out with certain concepts about histopathology, cytology, diagnosis, evaluation, prognosis, and treatment and their relation to cancer in situ of the uterine cervix. They state that the knowledge of the existence of cancer in situ dates back about forty years (Schottländer, 1907, and Schauenstein, 1908). The cytologic picture of cancer in situ is not as yet definitive. What is seen in the smear is the presence of cells with malignant characteristics in the cervical exfoliate. It is interesting to note that many times cells with malignant traits are seen in the cervical smear and yet it is impossible to find a cancerous lesion per se. The histological picture of cancer in situ is well known and is characterized by cancerous changes which do not go beyond the basal-cell structure and has no invasive characteristics. No doubt, the authors further state, future investigations will determine the true picture of the various categories of cancer in situ. From the clinical point of view there exist three possibilities: the asymptomatic form, the form concomitant with other lesions, and the form which may be suspected through minor trauma, leukorrhea, etc. The fundamental examinations for the diagnosis of cancer in situ are: Cytologic smear (Papanicolaou), colposcopy, Schiller iodine tests, and above all the circular tissue biopsy.

Cancer in situ may be present for months or even years as such. The prognosis of cancer in situ is excellent, close to 100 per cent if the treatment is adequate. The treatment of cancer in situ is based on the premise of complete eradication of the lesion.

The authors report on 22 cases of cancer in situ seen between 1936 and 1950. These cases were treated as follows: three by vaginal hysterectomy, one by simple trachelectomy and eighteen by the Wertheim procedure. The authors finish their article with a plea for establishing diagnostic centers throughout the country where complete diagnostic examinations may be available to the population at large.

RICARDO L. GORBEA

Cesarean Section

Noack, Hugdieter: Indications for Cesarean Section, Geburtsh. u. Frauenh. 12: 104, 1952.

At the University Clinic in Leipzig, a study of the indications and the results of operative deliveries has been made. In a series of 46,409 births, cesarean section was the method of choice in 1,114, thus giving an over-all operative delivery rate of 2.4 per cent. The indications for the use of cesarean section have been greatly broadened, especially where the life and welfare of the child were at stake. The author states that with the improvement in operative technique, together with the advantageous use of antibiotics, cases formerly considered not suitable for abdominal delivery could be delivered with ease and safety. The technique employed was usually of the classical type, with spinal anesthesia the best. Length of time in labor, the rupture of membranes, and the degree of dilatation of the cervix are no longer considered to be contraindications for cesarean section. In a review of the indications, cephalopelvic disproportion accounted for 60 per cent of the cases. Other reasons included eclampsia (7 per cent), placenta previa (14 per cent), and true fetal indications 6 per cent. A miscellaneous group (15 per cent) included placentae abruptio, ruptured uterus, etc. A total of 41 maternal deaths occurred (3.7 per cent), of which peritonitis accounted for 11 and extragenital infection for 6 cases, the remainder being caused by heart failure, ileus genital sepsis, emboli, and pneumonia. Over the years studied it is of interest to note that the mortality has decreased from 6.3 per cent in the earlier years studied to 0 in 1949-1950.

L. B. WINKELSTEIN

Cirne, Otto: Operative Obstetrics and Its Relation to Modern Anti-infectious Therapy, Ginecologia, August, 1951.

The author in a lengthy and voluminous paper discusses the effect of the advent of antibiotics and sulfonamides on the operative obstetrics of yesteryear. He brings out in a very detailed fashion the relative safety of present-day operative obstetrics with the aid of the "wonder drugs"

Cesarean sections done in greater numbers because of this new-found ally have lowered maternal and fetal mortality rates to almost zero. Pubiotomies and symphysiotomies for enlarging the pelvic outlet are not necessary now, cesarean section now being used in combination with the indicated antibiotic or sulfonamide. Extraperitoneal section, a difficult procedure in the hands of the average obstetrician has been obviated by preference for the transperitoneal low cervical procedure supplemented with antibiotics. The author, however, makes a plea for more continued vigilance by the obstetrician over his surgical technique and less dependence on the value of the anti-infectious therapy; in other words, let the antibiotics be an ally but never a substitute for aseptic surgical technique.

The author includes a bibliography with 102 references. The paper is illustrated with four charts.

RICARDO L. GORBEA

Extrauterine Pregnancy

Ribeiro, Edgar da Rosa: Abdominal Pregnancy, An. brasil. de ginec. April, 1952.

The author reports two cases of abdominal pregnancy in a very lengthy and meticulous manner. The first case, a nine months' gestation with a dead fetus, was complicated by a mechanical paralytic ileus; the second case, a three months' gestation complicated by a coexisting acute pelvic inflammatory condition, showed clinically only symptoms referable to the acute inflammatory process. Both cases were cured by surgical intervention with an uneventful postoperative course. The symptomatology, diagnosis, other coexisting conditions masking the abdominal pregnancy, as well as the etiology, pathogenesis, and treatment are discussed.

Several conclusions were drawn by the author. Among them were the following: (1) Abdominal pregnancy is of very infrequent occurrence. (2) The diagnosis is not easy to make, especially when coexisting conditions confuse the problem. (3) The diagnosis is all the more difficult when the pregnancy is an abdominal gestation from the beginning, without any previous symptoms of tubal abortion. (4) The history of the case should be meticulously taken and recorded, since it may lead to suspicion of the presence of an abdominal pregnancy. The diagnosis of a secondary abdominal pregnancy is based on the classical history of a previous tubal abortion. (5) In the case of a full-term pregnancy (abdominal) a hysterogram as well as the Pituitrin test would help in diagnosing the case correctly. (6) Great care must be taken in dealing with the placenta. Its removal, in the case of a live fetus, is a dangerous procedure, endangering the patient's life. With care one may resect it away from the underlying tissues and the raw bed left may then be cared for with sutures and Gelfoam or Oxycel. Another method is merely to remove the membranes, leaving the placenta in situ and closing the abdomen without drainage. In this case the cord should be cut and ligated close to the placenta. In the case of a dead placenta (with a dead fetus) its removal offers relatively little danger.

This paper is illustrated with several photographs and photomicrographs. The bibliography contains thirty-two references.

RICARDO L. GORBEA

Gynecology

Mollica, Jose: Ovarian Dysfunctions, O Hospital, vol. 2, No. 2, August, 1952.

The author, in this paper, reviews all the possible ovarian dysfunctions together with their effect on the menstrual cycle as well as the treatment instituted. The present knowledge of hormonal physiology, as well as its application in treating the various cases reported in this paper, is also brought forth. After this voluminous work, the author arrived at the following conclusions:

1. Contrary to what has previously been accepted, there occur more than one ovulation during each menstrual cycle, frequently two.

2. The two ovulations coincide with the two drops in follicular concentration in the blood, the first above 40 R.U. per liter, the second below 40 R.U. per liter.

3. The endometrial degeneration followed by menstruation is brought about by the rapid drop of high follicular concentrations in the blood to levels below 40 R.U. per liter.

4. The true follicular hormone present in the ovarian follicles is either estradiol, dihydrotheelin, di-hydroestrone, or di-hydrofolliculin. The other estrogens do not go beyond these metabolic changes.

5. Estradiol is the only estrogen that is capable of releasing all uterine physiologic activities as well as the changes observed during the menstrual cycle.

6. Excess follicule—hormonal dosage is injurious as it provokes pituitary blockage and disrupts the equilibrium not only of the pituito-ovarian hormones but also of the other normocrinic substances.

7. Therapeutic dosages of follicular hormones should be moderate, and an active preparation used when a stimulating or substituting effect is desired. Higher doses should be used only when an inhibitory effect is desired.

8. The best forms for administering the estrogens are: alcoholic solution of estradiol for oral use, and aqueous solution for the parenteral route.

9. The recent observations of Béclère and Zondek on the administration of small doses of hormones have shown nothing new; they only corroborate an old concept defended by the Italian gynecologists.

10. For the correct treatment of ovarian dysfunctions the clinician should have the necessary knowledge of the basic fundamentals of ovarian physiology.

This paper has a bibliography of 27 references and is illustrated with five charts.

RICARDO L. GORBEA

Filho, Goncalves de Azevedo: Present-day Status of Colpocytology, Rev. port. obst., ginec. e cir., May-June, 1952.

The author, in this very lucid and complete paper, discusses the present-day status and value of vaginal smear study related to hormonal activity. The technique of collecting the specimen, the various types of stains used, classification of the cytologic elements both normal and abnormal, from puberty to menopause and beyond, the definite relationship between the cytologic picture and the activity of the ovary (both estrogenic and luteal phases), as well as the importance of this knowledge in relation to future treatment, are all well brought out. The author has drawn the following general conclusions: (1) Colpocytology constitutes a practical and informative method of diagnosing hormonal activities in gynecology. (2) It helps in estimative estrogenic activity especially, and in orienting the gynecologist in the organotherapy indicated. (3) Thanks to its innocous quality, it makes it possible for repeated smears to be made on the same patient, and it can be used in virgins. (4) Colpocytology is of immense value in determining the causes of amenorrhea. (5) Colpocytology gives inestimable help as a method of evaluating ovarian repercussions in the presence of endocrine dysfunctions of other glands. The bibliography contains 96 references.

RICARDO L. GORBEA

Henriksen, Erle: Pyometra Associated With Benign Lesions of the Cervix and the Corpus, West. J. Surg. 60: 305, 1952.

A report upon pyometra which is based upon the clinical and laboratory experience in the management of 118 cases from the Los Angeles General Hospital and associated institutions would seem to offer opportunity for fairly complete coverage of the subject. When the report is clarified by the insertion of ten half-tone drawings beautifully and accurately executed, then it might be said that the subject has been adequately reviewed. Such is the nature of this paper.

Pyometra is a relatively uncommon clinical entity except in the presence of malignancy, it is thought and has been generally held. This is erroneous. The incomplete occlusion type is not rare and is often missed in the cursory gynecologic examination. Pyometra can be prevented in the great majority of cases by the careful application of the basic principles of good medical and surgical practice. A complete history, adequate examination, and limited use of the cautery, together with the postoperative and postdelivery care of cervicitis and the evaluation of cervical patency by passage of a sound within a period of six weeks following such procedures, will practically eliminate the condition.

Pyometra is potentially dangerous and should be considered a major surgical problem. It was the primary cause of death in 20 out of 118 patients here reported. The electrocautery is the most common single cause. The next is occlusion of the cervix secondary to atrophic changes of the menopause. Complications of pregnancy, especially criminal abortion, are occasionally followed by pyometra. It is a clinical condition too often overlooked and is so readily diagnosed by the simple passage of a uterine sound as an office.

procedure. Every cervix which has been subjected to any type of surgical procedure, in the office or in the hospital, should be followed by repeated passage of the uterine sound over a period of several weeks.

WILLIAM BICKERS

Wiseman, D. C., and Thomas, W. M.: Ovarian Denervation for Ovarian Dysmenorrhoea, Brit. M. J. 1: 141, 1952.

The authors believe that most of the sympathetic fibers which supply the ovary come from the tenth, eleventh, and twelfth dorsal segments and from the first and second lumbar segments, and pass through the infundibulopelvic ligament in association with the ovarian vessels. The patients under review did not have appendicitis or uterine dysmenorrhea. Reproduction of their pain was caused by bimanual compression of the ovaries. Operation consisted of clamping, cutting, and ligating the infundibulopelvic ligament close to the ovary on both sides. An incidental appendectomy, suspension, or resection of an ovarian cyst was done frequently, but was not considered to alter the outcome. It was not thought that the function of the ovaries was affected by the operation. Forty-nine per cent of the patients were cured while 44.5 per cent were improved and the remainder were unimproved. The failures were attributed to sympathetic fibers from the presacral nerve that reached the ovary via the uterine artery.

R. GORDON DOUGLAS

Wolskel, H. G., and Barnett, Vivian H.: The Treatment of Genital Tuberculosis in the Female by Streptomycin and Para-aminosalicylic Acid, J. Obst. & Gynaec. Brit. Emp. 59: 240, 1952.

The use is reported of streptomycin and PAS in the treatment of 12 cases of tuberculosis of the female genital tract; in all but one case, the diagnosis was made by histologic study and culture of the uterine curettings and guinea pig inoculation; in one case diagnosis was made by the histologic study of a Fallopian tube removed at operation. In the first case treated, strepomycin was given for only one month (on account of limited supply) and PAS was not available. In most of the other cases streptomycin was given for three months, but in 2 cases for four months, and in one case for five months. PAS was given for the same length of time in all but one of these cases, in which it was continued for six months. The dosage of streptomycin was 0.5 Gm. twice daily, and of PAS, 10 to 20 Gm. daily (according to tolerance). Guinea pig inoculation tests of uterine curettings were negative at the end of six months in 9 cases and had been negative at the end of three months in one other case not followed up later; in 5 cases, retested at the end of a year, the tests were also negative. Five of the patients complained of menorrhagia, which was entirely relieved in 4 cases, and improved in one; 2 who had amenorrhea showed a normal menstrual cycle after treatment. All but 2 patients showed a gain in weight; in one the weight remained unchanged, and in the other, weight loss was due to carcinoma of the Fallopian tube. In 2 cases adnexal masses subsided rapidly under treatment; in one case a mass became much smaller when PAS was continued for three months after streptomycin was discontinued. These results suggest that streptomycin and PAS may often replace surgical methods in the treatment of tuberculosis of the female genital tract.

HARRY B. MATTHEWS

O'Neil, Desmond: Uterine Bleeding in Tension States, J. Obst. & Gynaec. Brit. Emp. 59: 234, 1952.

This article reports 12 cases in which excessive uterine bleeding occurred without adequate organic cause, and in which the uterine bleeding was always associated with a tension state resulting from some stress or crisis in the patient's life. All of the patients had other symptoms of the tension state, such as depression, anxiety, headache, and fatigue. Three of these women had a masculine attitude and aims (one being a homo-

sexual) and showed other symptoms of the "Atalanta syndrome." All patients were given psychotherapy in an out-patient department. In 7 patients, menstrual function returned to normal and has remained so at the last follow-up. In 2, the symptoms improved, but abnormal bleeding recurred again when they were confronted with a new situation causing stress for which they were not prepared. The abnormal bleeding was reduced in amount in 2 patients, and in one the bleeding ceased with the menopause. These cases are briefly summarized, either in the text of the article or in the appendix.

HARVEY B. MATTHEWS

Botella Llusia, J., and Marin, E.: The Endometrial Biopsy; Its Technique and Interpretation, Acta ginec., Madrid 2: 257, 1951.

This is a comprehensive exposition of the technique of endometrial biopsy, its indications, and interpretation of results. The article is well illustrated with photomicrographs.

The optimum time for endometrial biopsy in the majority of cases is, according to the authors, just before the onset of menstruation, provided the woman has abstained from sexual intercourse from the eighth day of her cycle in order to be fairly certain that she is not pregnant. An early pregnancy, however, will not necessarily be interrupted by the procedure, and the authors quote Jackson as having described 36 cases in which endometrial biopsy was performed when an early pregnancy already existed (unknown to the operator but subsequently diagnosed). Only 5 of these women aborted.

Intramenstrual biopsy has the advantage of eliminating the chance of pregnancy and is a little easier to perform due to the slight cervical dilatation which occurs during menstruation, but has the disadvantage that the tissue obtained may be necrotic and histologic interpretation may be difficult.

The indications for endometrial biopsy are listed by the authors as follows:

1. Diagnosis of the anovulatory cycle, especially in sterility cases.

2. Diagnosis of ovarian endocrine abnormalities: (a) hyperestrinism; (b) hypoestrinism; (c) irregularities of the endometrial cycle, such as irregular maturation and irregular shedding of the endometrium.

3. Diagnosis of inflammatory conditions of the endometrium: (a) simple endometritis; (b) postabortal endometritis; (c) tuberculous endometritis, which accounts for 8 per cent of all cases of sterility.

4. Diagnosis of tumors, especially endometrial carcinoma. The authors emphasis that while a positive biopsy is diagnostic of endometrial carcinoma, a negative one has no value, as the site of the lesion may have been missed by the endometrial curette.

5. Diagnosis of processes related to gestation (abortive rests, ectopic pregnancy). While the suspicion of abortion is not an indication for endometrial biopsy, often the endometrial biopsy reveals an unsuspected abortion. Also, the finding of a decidual endometrium may point to a diagnosis of ectopic gestation.

MAGIN SAGARRA

Nogales, F.: Uterine Tuberculosis and Associated Lesions, Acta ginec., Madrid 2: 307, 1951.

The author has made a study of the association of uterine myomas and tuberculosis, showing that their coexistence is pure coincidence. He reports an interesting case of a myoma infected with tuberculosis, and another case in which the uterine tuberculosis invaded the capsule of a myoma but not the tumor itself. He also reports a case of fundal polyp infected with tuberculosis.

MAGIN SAGARRA

Ribeiro, Luis A.: Hemoperitoneum Caused by Rupture of Cyst of Corpus Luteum, O Hospital, vol. 42, No. 1, July, 1952.

The author in this paper relates the historical aspects of this condition, as well as discusses the etiology, incidence, macroscopic and microscopic anatomy, symptomatology,

diagnosis, prognosis, and treatment of the hemoperitoneum following rupture of the follicular and lutein cysts of the ovary.

A case of ruptured corpus luteum cyst with hemoperitoneum is reported by the author in a virgin 16 years of age with a preoperative diagnosis of acute appendicitis. There was found in the peritoneum about 300 c.c. of blood, and the mounted sections of the specimen removed showed the cyst to be luteal in origin. A chronic inflammatory process of the appendix was also found.

This paper has a bibliography with 29 references.

RICARDO L. GORBEA

Gynecologic Operations

Pernanbucano, Berilo: Study of Genitourinary Fistulas, Ginecologia, Nos. 1 and 2, January to April, 1952.

The author reports on 21 cases of vesicovaginal fistula, each of them with a history of prolonged labor and difficult delivery. In general, the fistulous openings measured between 1 and 2 cm. in diameter and were located near the bladder neck. The ages of these patients ranged from 17 to 42 years. Twelve of them were operated upon by the suprapubic route, 9 by the vaginal route.

Making a comparison of the final results in this series of cases, the author arrives at the conclusion that the vaginal route, with complete débridement of the fistulous tract, is the best method of approach and above all this technique is essentially gynecological.

The bibliography contains only one reference.

RICARDO L. GORBEA

Green-Armytage, V. B.: Tubo-Uterine Implantation, Brit. M. J. 1: 1222, 1952.

The author states that interstitial and isthmic sclerosis accounts for 82 per cent of tubal obstructions. This type of pathology is typical of "one pregnancy sterility" in which a history of a few days of puerperal fever may be elicited. The distal portions of such tubes are normal and capable of transmitting an ovum, whereas tubes obstructed at the fimbriated end suffer damage to the endosalpinx incompatible with normal function, even though patency be re-established. Surgery for the correction of interstitial and isthmic obstruction resulted in six term pregnancies in 17 patients operated upon by the author. The technique employed is essentially as follows: The point of obstruction is located by probing and the tube is amputated just distal to this point. The proximal end is split to form two lips 5 mm. long and 5 silkworm-gut sutures are attached to each lip. The occluded isthmus is removed along with a plug of myometrium by boring a tunnel through the cornu into the uterine cavity, a 9 mm. Silcox tubular punch being employed. The silkworm-gut sutures, attached to a needle, are then passed through this tunnel into the uterine cavity and back through the uterine wall. Traction is applied to the sutures and the split end of the tube guided into the endometrial cavity. The free ends of the silkworm-gut sutures are secured to the uterus and the external orifice of the tunnel gently sutured to the tubal serosa.

RANDOLPH GEPFERT

Lennon, G. G.: Stress Incontinence. A Preliminary Report on a New Method of Treatment, Brit. M. J. 1: 1384, 1952.

A simple operation, vesicourethrolysis, introduced by Mulvany, is used for the cure of stress incontinence. The original operation consisted of a complete mobilization of the urethra in the space of Retzius. This gave the sphincter area a greater degree of freedom which resulted in continence. No plication or other type of fixation or suspension is done. The author modified this in some of his later cases by accomplishing the mobilization through a Millin II incision between the clitoris and urethra. With the anterior vaginal wall opened,

the urethra can also be mobilized by rupture through the pudendal diaphragm which was also done in some cases. While the immediate results were good the author points out that a long follow-up is essential to assess the results properly. Of 23 patients subjected to the operation, 21 were cured as determined in the immediate postoperative period.

THOMAS L. BALL

Labor, Management, Complications

Hamilton, Hugh G., Higgins, Robert S., and Alsop, Webb S., Jr.: A Comparative Clinical Study of Naturally Derived and Synthetic Oxytocic Drugs of Ergot Origin, South. M. J. 45: 728, 1952.

Efforts to improve the routine management of the third stage of labor with the hope of reducing blood loss continue to be reported. A comparison has been made between the hemostatic effect of Methergine, a synthetic ergonovine, and the ergonovine derived from the natural alkaloids. No difference between them could be observed in the amount of blood loss during the third stage of labor when employed in like doses. Both are effective agents in controlling uterine contractions during the early puerperium. Ergonovine of natural origin, however, has much more pronounced effects upon the vasomotor system with resulting elevation of blood pressure. Whereas about 12 per cent of ergonovine patients showed a rise in blood pressure, only 1.8 per cent of patients who received Methergine showed such blood pressure elevations.

WILLIAM BICKERS

Mammary Glands

Zuckermann, C.: Mammary Phyllode Neoplasia, Acta ginec., Madrid, 2: 283, 1951.

The author presents a case of phyllode neoplasia of the breast operated upon in 1944 with apparent cure after seven years. The article is illustrated with actual photographs of the patient and photomicrographs of the tumor.

This type of tumor was first described by John Mueller in 1838. He called it "phyllode cysto-sarcoma" because of its "leafy" appearance on section, "phyllode" being a word of Greek origin meaning "leaf." The tumor has since been called by various other names, among them "giant intracanalicular fibro-adenomyxoma" by Lee and Pack.

Up to 1941 Lee and Pack had collected 111 cases from the world literature, and up to 1943 Cooper and Ackerman had collected 125 cases.

The author's case occurred in a woman of 48 years who had a tumor of the right breast of three years' duration when first seen. The growth was first noticed by the patient shortly after trauma to her breast; it progressed slowly for about two years, then had grown rather rapidly, particularly during the seven months preceding consultation. The tumor was only uncomfortable because of its weight. There were no pain, no axillary adenopathy, and no systemic changes. The opposite breast was normal and chest x-ray negative.

Radical mastectomy with axillary lymphadenectomy was performed. Histologic study revealed a tumor principally constituted by connective tissue with cancerization in limited areas. Other portions showed hyalinization, edema, infiltration, fibrosis, hemorrhage, and necrosis. In addition, there was neoplastic alteration of the epithelium of the ducts. The author believes that this type of tumor should be considered as benign, as it does not recur if extirpation is complete. He summarizes the habitual characteristics of phyllode neoplasia as follows: (1) long evolution, (2) large size, (3) no adherence or invasion of aponeurotic and muscular planes, (4) no propagation to axillary glands, (5) rarity of regional recurrence and absence of distant metastases, except in rare instances, (6) leafy appearance of sections, (7) histology of epithelial and especially connective tissue tumor with limited cancerization of the latter, (8) sometimes ulceration related to the

great development of the tumor, necrotic phenomena, and impaired cutaneous circulation, (9) favorable evolution and good prognosis after complete surgical extirpation.

MAGIN SAGARRA

Menopause

Alders, N., and Owen, T. K.: Oestrogen-Induced Haematometra and Haematosalpinx, J. Obst. & Gynaec. Brit. Emp. **59**: 214, 1952.

In the case reported, the patient was a woman 61 years of age; her chief complaint was abodminal pain; examination showed enlargement of the uterus. A total hysterectomy, with removal of both tubes and ovaries, was done; both the uterus and the Fallopian tubes were filled with gelatinous chocolate-colored fluid; the cervical canal was obliterated; sections of the wall of the cervix showed a small carcinoma with well-differentiated cells. The patient made a good recovery and is being kept under observation. The history showed that the patient had been taking estrogens for the relief of hot flashes for almost fourteen years; much of this time the estrogens were self-administered. She had never had vaginal bleeding since cessation of menstruation. The atresia of the cervix was considered to be due to local application of radium. The blood accumulating in the uterus and tubes is attributed to overstimulation of the uterine endometrium by prolonged administration of estrogens, combined with cervical atresia. This case illustrates the "injudicious" use of estrogens in the menopause.

HARVEY B. MATTHEWS

Menstruation, Dysmenorrhea

Medina, Jose B.: Dysmenorrhea, Ginecologia, October, 1951 and December, 1951.

The author, in this extensive and meticulously written paper which extends throughout two numbers of *Ginecologia*, discusses dysmenorrhea from all possible angles, reviewing the world literature on the subject, its etiology, symptomatology, and finally treatment. The treatment is always directed toward relief of the spasm. In cases of hypoplasia of the uterus associated with sterility the author has found the use of the estrogens an excellent method of relieving the painful menses. Presacral neurectomy, as well as bilateral ovarian denervation (by division of both infundibulopelvic ligaments), either singly or combined, was used to cure the intractable cases. The author also uses the androgens with their inhibitory action on the pituitary and ovary to relieve the dysmenorrhea but only until this product is stopped. Progesterone and the gonadotropins are also discussed in relation to their effect on the condition.

This paper has a bibliography with 69 references.

RICARDO L. GORBEA

Miscellaneous

Hunter, Oscar B., Jr., and Ross, John B.: Cortisone in Rh Incompatibilities, South M. J. **45**: 732, 1952.

On theoretical grounds erythroblastosis fetalis should be amenable to treatment with cortisone or ACTH. The disease involves an abnormal immunologic response and this is favorably modified by cortisone. An attempt to prevent the antibody rise in pregnant Rh-negative mothers who carry an Rh-positive fetus in the uterus is reported.

For unsensitized Rh-negative women cortisone was administered in a dose of 100 mg. at the time they went into labor. The hormone may be administered earlier in the unsensitized patient but a single injection seems to be adequate. In the treatment of sensitized Rh-negative mothers, delivery should be considered at the end of the thirty-eighth week. Corti-

sone is given in a daily dose of 100 mg. beginning at the thirty-sixth week and continuing to delivery. If the Rh antibody begins to rise around the thirty-eighth week, cortisone may be given in a dose of 50 mg. daily, the dose being based on the blood titer.

It is concluded by the authors that cortisone interferes with the antigen-antibody reactions of the Rh type and because of this fact offers some opportunity of preventing sensitization. Some sensitized mothers who have previously given birth to dead babies have borne living children in pregnancies wherein cortisone was administered. This is true despite the fact that the drug has apparently little effect in preventing antibody rise in the mother's blood. The unqualified statement is made that adequate cortisone levels during the last trimester in sensitized Rh-negative women will prevent hemolysis in the fetus.

WILLIAM BICKERS

Brand, Elizabeth: Bacteriology of Vaginal Flora After the Use of Internal Tampons, Brit. M. J. 1: 27, 1952.

A series of 100 women used vaginal tampons for protection during the menstrual period over three to ten successive periods in 57 cases, two monthly periods in 17 cases, and one monthly period in 26 cases.

Smears and cultures were taken before and after each period. No appreciable change in the bacterial flora of the vagina was noted after the use of tampons. Healing of erosion in 33 cases was unaffected. There was no evidence of local inflammation or irritation, no alteration of the pH or in the glycogen content of the epithelial cells.

The author concludes that there was no evidence that vaginal tampons are prejudicial to health.

WILLIAM P. GIVEN

Cusi Ramon, M.: Further Contributions in the Study of Fibromatosis Uteri, Toko-Ginec. Práct. 11: 51, 1952.

The author reviews 396 cases of uterine fibroids seen in his service during the past five years, 1947-1951. He points out and comments on the various methods used in the treatment of these cases at the Santa Cruz and San Pablo Hospitals. Statistically, the author brings out the relationship of infertility to the presence of myomas. The symptomatology in itself was found to be classical, alterations in the menstrual flow being paramount.

Treatment consisted primarily of surgical removal of the entire uterus, though a strong plea is made for more myomectomies in the presence of single tumors whenever possible. Fourteen cases were treated with radium. Four of these were followed by hysterectomy. There were five cases with coexistent malignancy, one cervical and four of the body of the uterus.

The author concludes his paper with the recommendation that prophylactic treatment should be instituted before the development of the tumor, following the theory of hormonal imbalance being responsible for formations of myomas. The author demonstrated this hormonal imbalance in 87.5 per cent of his cases. He believes that this hormonal disequilibrium is, if not the cause, the catalytic factor that predisposes to formation of myomas.

RICARDO L. GORBEA

Newborn

Bevis, D. C. A.: The Antenatal Prediction of Haemolytic Disease of the Newborn, Lancet 1: 395, 1952.

Although blood studies on Rh-negative women may show the possibility of hemolytic disease in the unborn child, actual probability is difficult to assay. As a prognostic test, the authors analyzed samples of amniotic fluid obtained by uterine puncture at the twenty-eighth week and every two weeks thereafter. In the extensive chemical survey, only the levels of urobilinogen and of nonhematin iron were of significance. Urobilinogen shows a sudden

but transitory drop in concentration when there is fetal disease. When the concentration of nonhematin iron is high, fetal disease is probable. These changes are evident at the thirtieth week, and appropriate clinical decisions can be taken at that time.

The uterine punctures caused no apparent damage to mother or child in any instance, nor did premature labor follow the procedure.

IRVING L. FRANK

Bodian, Martin, White, L. L. R., and Carter, C. O.: Congenital Duodenal Obstruction and Mongolism, Brit. M. J. 1: 77, 1952.

The authors report 32 cases of atresia or stenosis of the duodenum admitted to Great Ormond Street Hospital during the past 25 years. At least 10 of these infants were Mongols. During the year 1951, all 5 cases admitted were found to be in Mongols. The authors state that the association of these two conditions has not previously been reported in texts of surgery or pediatrics. The actual frequency of this complication in Mongolism, according to the authors, then probably exceeds their reported incidence of 1 in 3. A short summary of each of the 10 cases is cited.

R. GORDON DOUGLAS

Pregnancy, Complications

Rodringuez, Lopez B.: Death and Retention of Fetus in the Uterine Cavity During Pregnancy, Rev. port. obst. ginec. e cir. 5: 40, 1952.

The author, in discussing the problem of fetal death in utero, eliminates those cases of fetal death followed by expulsion of the ovum, for example, miscarriages of five or six months gestation, premature deliveries of dead fetuses of from six to nine months of gestation, and delivery at term of a dead fetus. In the first portion of his article the author explains all the various changes that the retained ovum may undergo: (1) hemorrhagic mold, (2) mummification, (3) maceration, (4) putrefaction, (5) petrifaction, (6) partial or total absorption.

The etiology is then outlined and divided into: (1) maternal, (2) paternal (3) ovular.

Maternal factors include: chronic infections, acute infection, endogenous toxic states (uremia, toxemias of pregnancy, diabetes), exogenous toxic states (nicotine, carbon dioxide, etc.), and the Rh factor.

Paternal factors include deficiencies of the chromosomic pattern in the sperm.

Ovular factors include torsion and knotting of the cord, placental separations, placenta previa, vascular lesions of the placenta.

The length of retention of the dead ovum is variable, ranging from a few days to three years (Voron). In diagnosing death in utero and retention of the ovum, the author recapitulates all the known classical signs and symptoms, as obtained through inspection, palpation, auscultation and x-rays, making mention of the different signs attributed to Spalding, Spangler, Horner.

The author divides the treatment of this condition into three schools:

1. Intervention and immediate evacuation of the uterine contents by direct or indirect methods. Here the author mentions the indirect method of Matthews, consisting of castor oil and quinine, followed by Pituitrin intramuscularly, and a somewhat direct method consisting of injecting 80 to 100 c.c. of hypertonic solution of salt or glucose through the abdomen into the uterine cavity. It is claimed that labor starts within 24 hours.

2. Nonintervention and letting nature expel the dead ovum.

3. The so-called eclectic school of intervention in some cases and not in others.

The author finishes his article with a strong plea for concentrated study of the cases of habitual abortion and repeated foetal death in utero to attack the sociological aspect of this problem.

RICARDO L. GORBEA

Palacios Costa, N., and Chavanne, F.: Incidence of Rupture of the Uterus, between 1934 and 1945, An. Ateneo Inst. matern. y asist. social **6:** 41, 1947-1948.

The authors report a series of 27 cases of reptured uterus out of a total number of 30,051 deliveries during a twelve-year period. These uterine ruptures were divided into traumatic (14 cases) and spontaneous (13 cases). Sixteen patients died. Ten of these cases were spontaneous ruptures and 6 were classed as traumatic ruptures. The most common cause of the traumatic rupture was internal version. Among the spontaneous ruptures, multiparity, previous section, and constitutional diseases (syphilis, typhus) were the most common causes. The authors declare there is no conservative treatment for ruptured uterus. The immediate emergencies (shock, blood loss, etc.) should be taken care of at the same time that the rupture is located. Site and size of rupture will determine whether a local repair or a hysterectomy (total or subtotal) is the treatment of choice. In closing, the authors recommend, as a means of avoiding these catastrophes, a more closely watched prepartum period and more of the venerable "watchful expectancy."

RICARDO L. GORBEA

Patterson, M., and Eytinge, E. J.: Chronic Ulcerative Colitis and Pregnancy, New England J. Med. **246:** 691, 1952.

The interaction of pregnancy and ulcerative colitis has been studied in sixteen women treated at the Lahey Clinic, by chart analysis and questionnaire. In six pregnancies which began during a remission of colitis, three patients felt that symptoms were unaltered, two thought that they were aggravated, and one felt that she was improved. In fifteen pregnancies (eight patients) which began during a mild or moderately active stage of colitis, the disease was aggravated in eight, unaffected in two, and relieved in five.

The pattern of alteration of symptoms of colitis during pregnancy does not follow the gastrointestinal effects of normal pregnancy (early irritability and late constipation). This may mean that factors other that exaggeration of normal responses are responsible.

The majority of women who become pregnant while colitis is quiescent have minimal difficulty, although it is difficult to predict individual reaction. Therapeutic abortion should be warranted only in rare instances. In contrast, the course of colitis occurring for the first time during pregnancy is likely to be fulminating. These patients demand careful observation, and early ileostomy should be considered. Of five patients in this group, one required ileostomy two months post partum, and one died as a direct result of her disease after a delivery at six months. This picture is confirmed in three cases reported by Tumen and Cohn. The fetal salvage rate is low, and there is little evidence that spontaneous abortion improves the situation.

IRVING L. FRANK

Fouracre Barns, H. H. and Morgan, M. E.: Pregnancy Complicated by Diabetes Mellitus, Brit. M. J., Jan. 8, 1949.

A series of 58 diabetic pregnancies in 45 patients is reviewed. The authors' experience coincides with that of most observers in the field. They found that insulin requirements usually increase in pregnancy and diminish sharply in the neonatal period. A high incidence of hydramnios (29 per cent) and toxemia (43 per cent) was found, as well as a difficulty in controlling the diabetes in a number of patients. One maternal death associated with diabetic acidosis and epileptiform convulsions is reported. The exact cause of the death is unknown.

Fifteen of the 58 patients were treated with estrogen therapy. Of the 43 patients who did not receive hormone replacement therapy, one patient was lost, 2 aborted, 13 had intrauterine fetal death, and 9, neonatal death. The total fetal mortality was 55 per cent. The authors state that toxemia, acidosis, and hypoglycemia are not primarily responsible for the fetal death, pointing to the high fetal mortality in the prediabetic patients.

The second series of 15 diabetic pregnancies were treated with estrogen and early termination of the pregnancy was avoided in all but two cases. There were one stillbirth and

two neonatal deaths, a total mortality of 20 per cent. The authors contend that these results suggest the efficiency of hormone replacement therapy.

Finally congenital deformities, gigantism, and hypoglycemia of the newborn are briefly discussed and it is suggested that the tendency to gigantism is due to excess of the growth hormone from the pituitary gland of the mother.

WILLIAM P. GIVEN

Gilbert, J. A. L., and Dunlop, D. M.: Diabetic Fertility, Maternal Mortality and Fetal Loss Rate, Brit. M. J. **1**: 48, 1949.

The authors state that insulin therapy has increased the fertility of diabetic women and has made pregnancy a relatively safe procedure, for the mother, but has failed to produce a very significant decrease in the fetal mortality rate in diabetic women.

The prediabetic obstetrical histories of 165 women, in whom diabetes was diagnosed between the ages of 25 and 69 years, are analyzed. The over-all prediabetic fetal loss rate was 15.7 per cent compared to the nondiabetic control group of 8 per cent.

In those patients in whom diabetes was diagnosed before the age of 45, the prediabetic fetal loss was 24.2 per cent. On the whole, the authors state, there is a progressive increase in the fetal loss rate as the time when diabetes is first diagnosed is approached. The maximum prediabetic fetal loss rate, occurring in the two years before the diagnosis of diabetes was made, was 50 per cent for young diabetics, a rate which was as high as that observed after the onset of clinical diabetes.

In those patients in whom the diabetes was diagnosed after the age of 45, the prediabetic fetal loss rate, which in this group was one and one-half times the nondiabetic control rate, failed to show the dramatic rise, immediately before the diagnosis of diabetes, observed in the younger group of women.

The authors conclude, from their study, that the factors responsible for the large babies, the high fetal loss rate, and the ensuing maternal diabetes have a common basis in some general metabolic disturbance in the mother and that the features of clinical diabetes, such as polyuria, glycosuria, thirst, etc., are a very late stage of this metabolic disturbance, an early feature of which is a high fetal loss rate.

WILLIAM P. GIVEN

Keynes, Geoffrey: Obstetrics and Gynaecology in Relation to Thyrotoxicosis and Myasthenia Gravis, J. Obst. & Gynaec. Brit. Emp. **59**: 173, 1952.

Thyrotoxicosis often causes menstrual disturbances in women, most frequently amenorrhea; such disturbances are less frequent in the milder forms of toxicity than in the more severe forms. Relative sterility is common in women with hyperthyroidism, yet pregnancy occurs in cases of relatively severe thyrotoxicosis. In the treatment of thyrotoxicosis in pregnancy, the use of radioactive iodine is contraindicated. With the purpose of avoiding operation during pregnancy, thiouracil has been used in the treatment of hyperthyroidism in pregnant women, but this has been found to result in congenital goiter in the infant in a number of cases. Illustrative cases are reported. Thyroidectomy may result in abortion if done in the first three months of pregnancy, but later in pregnancy, with the use of modern methods of preoperative preparation, it may be done safely. At the North End Thyroid Clinic of London, subtotal thyroidectomy was done on 18 women during the third to the seventh month of pregnancy; iodine was used for preoperative preparation; and the use of thiouracil was avoided in all but 2 cases. All patients were delivered normally with only one stillbirth. At St. Bartholomew's Hospital partial thyroidectomy was done in the third to the fifth month of pregnancy in 3 cases with good results. Eight women with hyperthyroidism operated on later had normal pregnancies. In cases of thyroid deficiency, menorrhagia may occur but thyroid medication results in improvement; in cretinism and juvenile myxedema, sexual maturation is delayed, but this also is improved by thyroid medication. Pregnancy does not often occur in women with thyroid deficiency, but, if it does, carefully controlled thyroid therapy is indicated.

Myasthenia gravis is preponderantly a disease of women; in the author's series of 326 patients, 147, or 65 per cent, were women. Comparatively few cases of pregnancy in women with myasthenia gravis have been reported. In a series of cases studied, 27 pregnancies had occurred. In 17 in which pregnancy occurred before thymectomy had been done, 10 showed improvement in the symptoms of myasthenia, 4 became worse, 3 showed no change; in 8 in which pregnancy occurred after thymectomy, 4 improved, 3 being completely relieved of symptoms, 1 became worse, and 3 showed no change. In the 27 pregnancies there were 25 normal infants (including one pair of twins); labor was induced in 2 cases and a miscarriage occurred in 1 case.

HARVEY B. MATTHEWS

Browne, O'Donel: Toxaemic Accidental Hemorrhage, J. Obst. & Gynaec. Brit. Emp. **59:** 153, 1952.

In a study of 100 cases of so-called toxemic accidental hemorrhage, it was found that the hemorrhage was not associated with toxemia in all cases; 26 of the cases were true accidental hemorrhage with shock but without toxemia. Vaginal examination in 95 women showed that in 24 who were in labor on admission, 15 infants were stillborn, in the 69 cases in which the patient was not in labor on admission, 62 infants were stillborn. There were 7 maternal deaths, all occurring in women not in labor at the time of admission. All these 7 patients were in Phase II (complete separation of the placenta) with the fetus dead in utero, when admitted to the hospital, and all were in shock. The shock was preceded by toxemia in 4 of these cases and by chronic hypertension in 2, while one was a case of true nontoxic accidental hemorrhage. The high fetal and maternal death rate in this series leads the author to conclude that earlier active antishock treatment by blood transfusion in Phase I (incomplete separation of the placenta) and prompt transmission to the hospital are essential. Nurses, doctors, and medical students should be instructed in the early recognition and prompt treatment of antepartum hemorrhage in its early stage. By this method the development of Phase II may be prevented. If the woman is in Phase II when admitted, unless the blood pressure readings, the increase in urinary output, and the patient's general condition indicate that shock is being controlled, and unless labor has definitely begun, lower segment cesarean section should be done without delay. The cesarean section should be preceded by adequate blood transfusion (3 pints). Cesarean section may also be indicated in some cases in Phase I and should be done promptly in such cases.

HARVEY B. MATTHEWS

Pregnancy, Physiology

Sanchez, T. Martinez: Diseases and Anomalies of the Glands of Internal Secretion During Pregnancy, Toko-ginec. práct. May, 1952.

This paper covers both the normal and abnormal hormonal changes in the glands of internal secretion during pregnancy. The author defines the changes necessary for pregnancy to continue its course normally as the nonpathological or physiological "normal" changes. The true pathological changes complicating pregnancy are classified as "abnormal" or nonphysiologic.

All the glands of internal secretion are discussed (thyroid, parathyroids, suprarenals, pituitary, pineal body and thymus, and pancreas). Basedow's disease, as well as hypothyroidism, is discussed. Symptomatology and treatment are outlined, as well as the effects of these conditions on the pregnancy and its ultimate outcome. The conditions involving the anterior and posterior lobes of the pituitary gland are brought out, and treatment involved is outlined. The same is done with Addison's disease and tetany. The paper ends with a length discussion of diabetes and its effect on the mother and fetus. The therapeutic approach is outlined in a very thorough manner.

The author includes a bibliography with 16 references.

RICARDO L. GORBEA

Christensen, R. C., Margulis, R. R., and Stewart, H. L., Jr.: The Effect of ACTH and Cortisone on the Rh Antibody Titer During Pregnancy, West. J. Surg. 60: 429, 1952.

Isoimmunization with one of the Rh factors is the important factor in the development of erythroblastosis fetalis. Ten pregnant patients were treated with ACTH or cortisone, the hormones being given intramuscularly in divided doses. The dose varied with the amount necessary to depress the antibody titers. Generally 75 to 100 mg. of either hormone was given at intervals of 3 to 6 times a week. When the titer did not show satisfactory suppression with the intramuscular injection, the intravenous administration of ACTH was substituted.

It is hypothecated that ACTH and cortisone may reduce the antibody titer by blocking the antigen-antibody union. However, it is well known that the height of the Rh antibody titer is not necessarily related to the degree of erythroblastosis fetalis. Since this is true and since ACTH or cortisone is not harmful when given to pregnant women over prolonged periods, there would appear to be no need to withhold the hormones during pregnancy.

The authors conclude that whereas it is possible to reduce antibody titers in pregnancy the severity of the hemolytic process is probably not altered. Of the ten babies delivered from ten mothers where there was Rh incompatibility and wherein all the mothers were treated with either ACTH or cortisone, there were two babies who died in utero in the sixth and seventh months of pregnancy with evidence of erythroblastotic changes. The results are statistically inconclusive as to the value of ACTH or cortisone in the prevention of erythroblastosis.

WILIAM BICKERS

Miller, R. A., and Crombie, J. D.: The Plasma Blood Cholesterol and Plasma Blood Potein of Lactating Women, J. Obst. & Gynaec. Brit. Emp. 59: 226, 1952.

A determination of plasma cholesterol and plasma albumin and globulin was made in 83 women who were lactating adequately, 25 who were lactating but inadequately, 26 women who had ceased to lactate within a week after delivery and 25 controls, normal women in the same age group. In the women who were lactating adequately between the third week and fifth month after delivery, there was a definite hypercholsterolemia; in the women who were not lactating adequately and in those who had stopped lactating six or seven weeks before the test was made, there was also a hypercholesterolemia not differing significantly from that observed in lactating women with infants of the same age. These findings indicate that hypercholesterolemia is an effect of pregnancy rather than of lactation. While a relatively low plasma albumin level was found in women within two weeks after delivery, in the third to the fifth week after delivery, the plasma albumin level was similar to that of the normal controls and it was not related to the adequacy of lactation, indicating that the hypoproteinemia of the early puerperium is an effect of pregnancy or of pregnancy and parturition. In the first month after delivery, the plasma globulin was lower than in the normal controls; in this period the plasma globulin values were greater for those with inadequate lactation than for those with adequate lactation. From the second to the fifth month after delivery the plasma globulin level was not significantly different from that of the controls, whether lactation was adequate or inadequate, or had ceased for six or seven weeks. Further investigation of the relation of plasma globulin to lactation is necessary, as other investigators have reached conflicting conclusions in this respect.

HARVEY B. MATTHEWS

Toxemia

Finnerty, F. A., Jr.: Hypertensive Toxemias of Pregnancy (Simplified Management With an Extract of Veratrum Viride), New England J. Med. 246: 646, 1952.

The author presents the results of treatment with an extract of veratrum viride (Vergitryl, Squibb) in 122 cases of hypertensive toxemia. These included 8 cases of convulsive eclampsia, 36 cases of mild eclampsia, 17 cases of moderate to severe pre-eclampsia, 45 cases

of essential hypertension with superimposed toxemia, and 46 cases of postpartum toxemia. Excellent results (defined as a prompt blood pressure fall, relief of symptoms, and a living fetus) were obtained in about 80 per cent of cases.

Since the dosage level and frequency vary with the individual, the author describes in detail the method of reaching therapeutic levels. Vergitryl, 0.75 units, is the average effective intramuscular dose. It shows its hypotensive effect in 30 minutes, reaching peak effect in 45 minutes. Duration of hypotension varies from 1 to 8 hours, average 3½ to 4 hours. If the initial dose is ineffective after 1 hour a dose of 0.9 unit is used. The dose is repeated at whatever frequency is necessary to maintain blood pressure under 140/90.

For the rapid effect necessary in eclamptic patients the drug is administered intravenously in divided doses through a polyethylene catheter. Possible systemic toxic effects, probably due to vagal stimulation, include salivation, nausea, vomiting, and diarrhea. These are effectively countered by the use of 50 mg. of pentobarbital sodium intravenously. There are no recorded deaths from use of the drug.

The exact mode of action of veratrum remains undetermined. There is stimulation of afferent vagus endings in the heart and in the carotid sinus. The end effects are vasodilatation and bradycardia. The bradycardia may be abolished by atropine and the hypotension can be overcome by ephedrine. Transient oliguria, once felt to be a bad side effect, is actually followed by a marked polyuria. The author feels that the excellent results from several reports (summarized to one death in 196 cases of eclampsia), lack of depressant effect on the fetus, and the current availability of well-standardized extracts warrant a wider use of the drug.

IRVING L. FRANK

Erratum

In the article, "The Effect of Stigminene Bromide in Delayed Menstruation," by Albert Decker in the November issue of the JOURNAL, page 1137, the spelling Stigminene is used throughout. The preferred spelling is Stigmonene.

Items

"The Foundation Prize" of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons

Rules governing the award of "The Foundation Prize" are as follows:

1. The award, which shall be known as "The Foundation Prize," shall consist of $200.00.

2. Eligible contestants shall include only (a) interns, residents, or graduate students in obstetrics, gynecology, or abdominal surgery, and (b) persons with an M.D. degree, or a scientific degree approved by the Prize Award Committee, who are actively practicing or teaching obstetrics, gynecology, or engaged in research in these fields."*

3. Manuscripts must be presented under a nom de plume, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the nom de plume and containing a card showing the name and address of the contestant.

4. Manuscripts must be limited to 5,000 words, and must be typewritten in double spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

5. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the official Journal of the Association or, failing that, in a Journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

6. Three copies of all manuscripts and illustrations entered in a given year must be in the hands of the Secretary before June 1.

7. The award will be made at the Annual Meeting of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

8. The President of the Association shall annually appoint a Committee on Award, which, under its own regulations, shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting.

WILLIAM F. MENGERT, M.D.
Secretary
2211 Oak Lawn Avenue
Dallas, Texas

Postgraduate Seminar in Obstetrics and Gynecology

This course, to be held April 10 and 11, 1953, will consist of teaching sessions conducted by the guest speakers, which will be of interest to specialists and general practice physicians and will review the common gynecological and obstetrical problems encountered in practice.

The guest speakers will be: William F. Mengert, M.D., Conrad G. Collins, M.D., and Woodward D. Beacham, M.D.

UNIVERSITY OF COLORADO MEDICAL CENTER
4200 East Ninth Avenue
Denver, Colorado

*Addition to Paragraph 2. (Approved September 4, 1952):
No fellow of the Association shall be eligible to compete for this Prize, and no candidate securing the award shall be eligible to compete again.

Ovarian Tumor Registry

While the Ovarian Tumor Registry of the American Gynecological Society is known to many gynecologists and pathologists, there are probably a good many who are still not familiar with its purposes and its methods of procedure. As was announced in most of the special medical journals in 1942, the Registry was created for the collection, authentication, and long-range study of ovarian tumors, with emphasis on those of rare type, as well as the more common varieties concerning which our knowledge is still very incomplete (carcinomas, cystadenomas, etc.). Already considerably more than 1,200 such tumors have been registered, including more than 200 of the feminizing group, and 60 of the masculinizing varieties, so that the Registry is probably already the world's richest storehouse of such material. Now that a sufficiently long follow-up period has elapsed with some of the categories, they are being intensively studied by competent pathologists under the sponsorship of the Ovarian Tumor Committee, and publication of these studies will soon begin.

It is hoped that more and more clinics and laboratories will cooperate by sending in representative slides or gross material of interesting ovarian tumors, with accompanying clinical data. Regular Clinical Forms to facilitate and systematize the latter are obtainable from the Chairman of the Committee, Dr. Emil Novak, 26 East Preston Street, Baltimore, to whom all material for the Registry may be forwarded. While the Registry makes no pretense of rapid diagnostic service, material is promptly acknowledged, with the preliminary personal impression of the Chairman before the more deliberate collective study of the entire committee.

For the first few years of its existence the Financial support of the Registry came from the sponsoring organization, the American Gynecological Society, and for the last three years the increasing burden has been met by a grant from the American Cancer Society. Beginning on Jan. 1, 1953, the financial support of the Registry has been taken over by the Academy of Obstetrics and Gynecology, as a part of its program of advancement of knowledge of obstetrics and gynecology in every feasible way. This generous annual grant made by the Academy is deeply appreciated by the American Gynecological Society and its Ovarian Tumor Committee.

Robert F. Faulkner
George H. Gardner
Karl H. Martzloff
Herbert F. Traut
Emil Novak, Chairman, Ovarian Tumor Committee